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Original Communications

THE LEAD VECTORS OF MULTIPLE DIPOLES LOCATED ON A TRANSVERSE PLANE OF FRANK'S HOMOGENEOUS TORSO MODEL

ROBERT A. HELM, M.D.

CINCINNATI, OHIO

ASSUMING the validity of representing the electromotive forces of the heart by means of a single dipole of fixed location and variable moment, the electrical properties of the heart and any number of electrocardiographic leads may be defined vectorially. The deflection pattern recorded by a lead is determined by the magnitude of successive instantaneous scalar products of the variable heart vector and the constant lead vector. This basic concept, first formulated by Burger and Van Milaan[1] may be extended by considering an electrocardiographic lead to consist of multiple vectors, one for each separate point in the myocardium where an electromotive force is generated.[2] The hypothesis of a fixed equivalent dipole is then no longer necessary.

An electrocardiographic lead would be ideal for use in vectorcardiography if its constituent vectors, for all portions of the heart, were of identical magnitude and direction.[3] If such leads could be developed, the sum of all of the electromotive forces produced by the heart at any single instant could be recorded and represented as a single spatial vector without making any assumption concerning the controversial dipolelike property of the heart. A statistical method was previously devised to express quantitatively the variation of a lead from one with ideal vectorcardiographic properties and to determine the probability that one lead was superior to another for vectorcardiographic recording.[3] In order to apply this statistical method to conditions grossly simulating the human

From the Cardiac Laboratory, Cincinnati General Hospital and Department of Internal Medicine, College of Medicine, University of Cincinnati, Cincinnati, Ohio.

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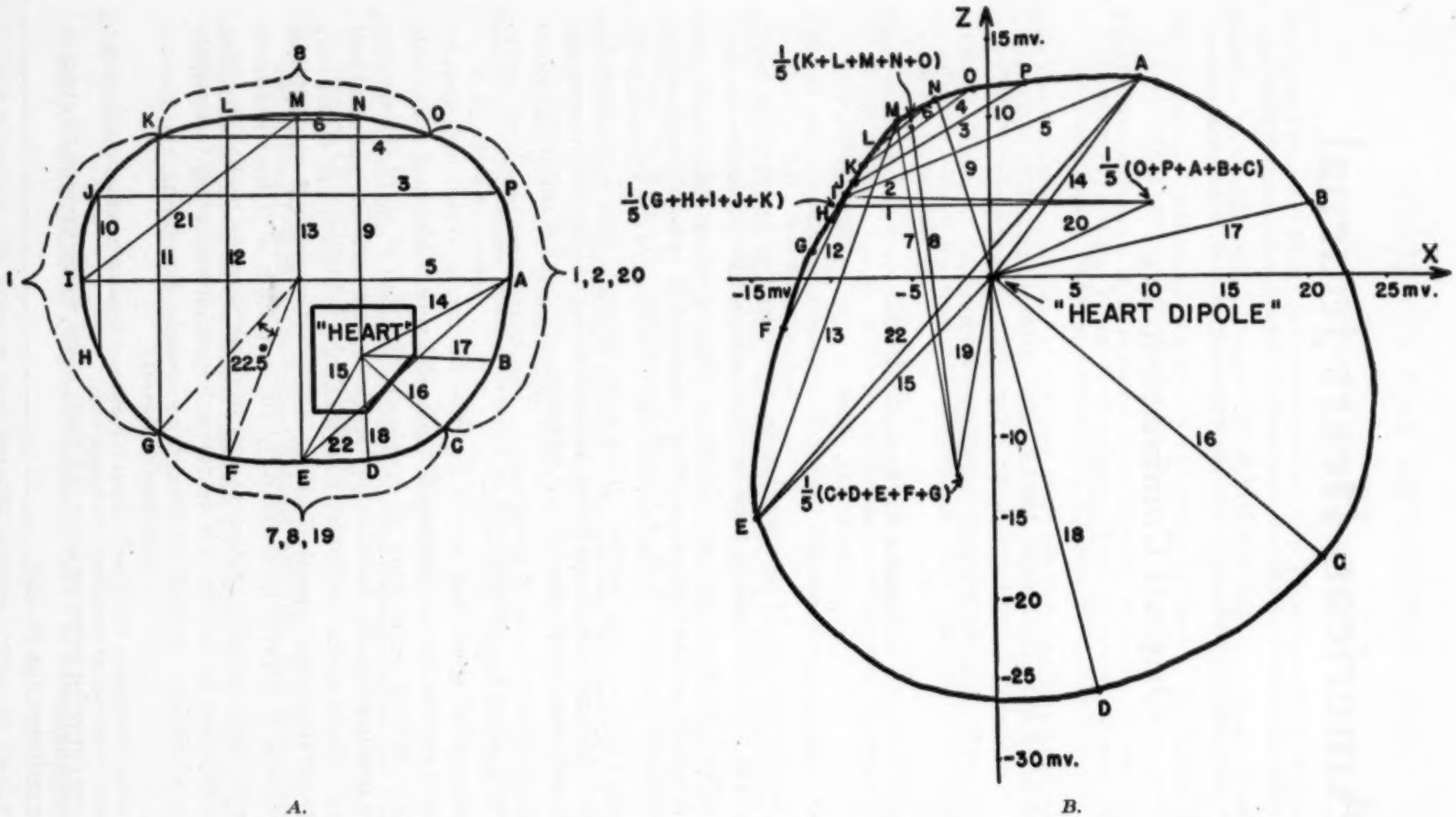

A. *B.*

Fig. 1.—*A*, anatomic cross-section of thorax. *B*, cross-section of thorax in image space based on mean potentials of the "heart." The 71 dipole positions are located in the area designated in *A* as "Heart." In *B* the 71 dipoles are arbitrarily reduced to a single mean dipole and the image loop is determined by the x and z components of the mean potentials of points *A* through *P*, plotted in millivolts. In both *A* and *B*, the numbers designating the anatomic and electric lead axes correspond to those given in Table I. (In *B*, due to the proximity of points *G* through *L*, the axes of Leads 10, 11, and 21 could not be conveniently included.) See the text and Table I concerning the relative degree of validity of the single dipole representation for each of the 22 leads illustrated. (After Frank.[4])

body as a volume conductor, the potentials which would be developed by multiple dipoles located on a circular electrically homogeneous lamina were calculated. From these data, the magnitudes and directions of multiple vectors, one for each dipole, were determined for a wide variety of leads applied at the circumference of the lamina. It was shown that, for the conditions postulated, a lead between two networks of points, suitably located on the circumference, was greatly superior, from a vectorcardiographic standpoint, to any lead between two single points.[3]

After this work had been completed, Dr. Ernest Frank published data relative to the potentials recorded on the surface of his torso model when an artificial dipole was placed at various locations within the model.[4] Specifically, a dipole was located at seventy-one separate points in a plane of the model, the dipole was alternately oriented transversely and sagittally, and the voltages developed at sixteen points at the periphery of this same plane were measured against a fixed reference potential.[5] Thus, the x and z components of each dipole position were measured; Frank showed that the y component was always extremely small in comparison to the other two and could, therefore, be disregarded.

The seventy-one positions of the dipole are illustrated in Fig. 9 of Frank's publication[4] to which the reader is referred. The area enclosing these dipole positions occupies the approximate region of the cross-sectional area of the heart at this transverse level. Point A is located in the left midaxillary line, and, proceeding in a clockwise direction, points A through P are arranged about the periphery of the cross section of the model in such a manner that lines joining these sixteen points with the center of the section form angles of 22.5 degrees (see Fig. 1,*A*).

METHODS AND NOMENCLATURE

The x and z potentials developed by each of the seventy-one dipoles at each point, A through P, were converted to millivolts by dividing the respective tabular values listed in Table I of Frank's publication by ten times the normalization factor at the top of each column.[4] From these data the x and z components of the wide selection of leads listed in Table I of this communication were calculated. As explained in detail in the previous paper,[3] the variation of a lead from one which has completely uniform vectors, may be calculated from the equation,

$$C = \sqrt{\frac{10^4 n}{(2n-2)} \left\{ \frac{n(SX^2 + SZ^2)}{(SX)^2 + (SZ)^2} - 1 \right\}}$$

where C is the coefficient of variation in percent, n is the number of dipoles, SX^2 is the sum of squares of the x components, $(SX)^2$ is the square of the sum of the x components, and the Z terms have corresponding definitions.

In Table I the leads studied are designated by letters in accordance with Fig. 9 of Frank's publication.[4] For convenience the leads are also numbered. The leads are arranged in groups which may be clarified by referring to Fig. 1,*A*. Leads 1 through 6 parallel the x axis anatomically while Leads 7 through 13 similarly parallel the z axis. The third group, consisting of Leads 14 through 18, is composed of unipolar leads recorded from points in the precordial region with the

TABLE I

LEAD NO.	LEAD	$\bar{x}$ (MV.)	$\bar{z}$ (MV.)	$\bar{l}$ (MV.)	"DISTURBING COEFFICIENTS" $\pm 100\ \bar{z}/\bar{x}$ (%)	"DISTURBING COEFFICIENTS" $\pm 100\ \bar{x}/\bar{z}$ (%)	C (%)	C^2 ($\times 10^4$)
1	1/5(O+P+A+B+C)−1/5(G+H+I+J+K)	19.61	0.02	19.61	0.1		14.3	204.1
2	1/5(O+P+A+B+C)−I	19.30	− 0.47	19.30	2.4		14.7	215.5
3	P−J	10.83	6.07	12.42	56.0		26.0	676.7
4	O−K	6.95	4.76	8.43	68.5		28.5	813.1
5	A−I	18.31	7.14	19.66	39.0		29.9	895.1
6	N−L	3.61	2.80	4.57	77.6		33.0	1091.3
7	1/5(C+D+E+F+G)−M	3.30	−21.94	22.18		15.0	16.8	283.5
8	1/5(C+D+E+F+G)−1/5(K+L+M+N+O)	2.55	−21.64	21.79		11.8	17.7	312.5
9	−N	3.52	−11.23	11.77		31.3	26.7	714.6
10	H−J	− 1.57	− 2.29	2.78		68.6	32.0	1024.5
11	G−K	− 3.23	− 5.38	6.27		60.0	33.5	1124.5
12	F−L	− 5.99	−11.43	12.91		52.4	37.4	1398.5
13	E−M	− 9.35	−25.38	27.05		36.8	46.6	2175.7
14	A	9.44	12.44	15.62	131.8		37.1	1378.8
15	E	−15.14	−15.36	21.57		98.6	55.0	3023.3
16	C	20.78	−17.09	26.90			56.8	3220.3
17	B	20.25	4.78	20.81			57.5	3306.4
18	D	6.12	−25.86	26.57			65.5	4286.0
19	1/5(C+D+E+F+G)	− 2.49	−11.92	12.18		20.9	23.4	549.1
20	1/5(O+P+A+B+C)	10.42	4.84	11.49	46.4		29.0	838.7
21	M−I	3.09	4.71	5.64			30.5	933.4
22	A−E	24.58	27.80	37.11			30.7	943.6

assumption, entirely theoretic, of an "indifferent electrode" of zero potential for all seventy-one dipole locations. (Lead 9 is also a unipolar lead analogous to sagittal Lead V_B of the tetrahedral system.) Leads 19 and 20 are unipolar leads in which the "indifferent electrode" is assumed to be consistently zero for all dipoles and the "exploring electrode" consists of a network of five points. Finally Leads 21 and 22 are included to illustrate an interesting finding which will be discussed below. In the $\bar{x}$ and $\bar{z}$ columns of Table I are listed the mean x and z components in millivolts of each of the leads for the seventy-one dipole locations and in column $\bar{1}$ the mean magnitude of each lead is given in millivolts. In the columns designated by the term, "disturbing coefficients"* the percentage calculated by the quantity, $\pm 100\ \bar{z}/\bar{x}$, expresses the average degree to which the anatomically transverse leads are mingled with sagittal components, and similarly the quantity, $\pm 100\ \bar{x}/\bar{z}$, expresses the average degree to which the anatomically sagittal leads are mingled with transverse components. The quantity C expresses the coefficient of variation in per cent as previously defined. The leads in each group are listed in the order of increasing values of C. Finally, in the last column, the values of C^2 are given in order to determine the probability that one lead is superior to another for vectorcardiographic recording. If the ratio of the larger to the smaller of the C^2 values of the two leads exceeds 1.69, the probability is less than 0.2 per cent that this could have occurred by chance.[7] Attainment of such a probability level denotes a high degree of statistical significance.

RESULTS

Lead 1 records the average potential difference between a newtork of 5 points, O, P, A, B, and C, joined through equal resistors and a similar network of 5 points, G, H, I, J, and K. From a vectorcardiographic standpoint, this would appear to approach an ideal vectorcardiographic lead since its coefficient of variation is relatively low (14.3 per cent) and its "disturbing coefficient" is nil. Lead 2, which differs from Lead 1 in that the single point, I, is substituted for the network of 5 points on the right side of the chest, has a coefficient of variation which is practically identical with that of Lead 1. The degree of lead vector uniformity of these leads is much superior to that of any other lead in this group as is obvious from a perusal of the C^2 values.

Although located on the plane of the dipoles rather than at a more caudad level, Leads 3 through 6, and particularly Lead 4, are analogous in their anatomic orientations to the transverse leads of the cube system of Grishman and Scherlis[8] and the "double cube" system of Duchosal and Sulzer.[9] It is of interest that these leads not only have considerably larger coefficients of variation than Leads 1 and 2 but also record average z components which are substantial in comparison with the average x components which they purport to measure. It should also be noted that there are no highly significant differences in the coefficients of variation of Leads 3 through 6, and, particularly, that the magnitude of C does not correlate with the relative degree of proximity or remoteness of the lead

*This descriptive term was introduced by Frank to designate his method of handling an analogous problem.[6]

electrodes from the dipole cluster. (This finding will be commented on below in connection with Leads 21 and 22.) Finally, the reader will note that the mean magnitudes of network Leads 1 and 2 are approximately the same as the $\bar{I}$ value of Lead 5 and definitely greater than the mean magnitudes of Leads 3, 4, and 6 whose electrodes are more distant from the dipole cluster, again confirming, as discussed previously,[3] the experimental findings of Johnston and McFee.[10]

Among the second group of leads which parallel the z axis anatomically, Leads 7, 8, 10, 11, 12, and 13 correspond respectively to Leads 2, 1, 6, 4, 3, and 5 of the first group. In general, the same conclusions may be drawn with respect to this group of anatomically sagittal leads as pointed out for the group of anatomically transverse leads except that in the case of Leads 10 through 13 there is a correlation between an increasing coefficient of variation and increasing proximity of the electrodes to the dipole cluster. Lead 9, representing the unipolar potential of point N with reversed polarity, is included because of its analogy to Lead V_B of the tetrahedral system. Its characteristics (C and $\pm 100\,\bar{x}/\bar{z}$) are distinctly inferior to those of Leads 7 and 8. Its apparent superiority over Leads 10 through 13 may be an illusion as far as comparison of the sagittal leads of the cube and tetrahedral systems are concerned. Since point N is relatively remote, the potential of the Wilson central terminal would be relatively large in comparison with the potential of N. In the previous publication dealing with the homogeneous circular lamina, it was found that the substitution of a central terminal for a theoretically indifferent electrode of zero potential consistently and significantly increased the size of C when the "exploring electrode" of such a lead was relatively remote.[3] It is possible, indeed likely, that the same phenomenon would occur here.

The unipolar precordial Leads 14 through 18 also postulate the use of an indifferent electrode of zero potential, but, since the potentials of points A through E are quite large, the substitution of the Wilson central terminal as the indifferent point would have very little effect on the characteristics of these leads.[3] Leads 14 through 18 possess quite large coefficients of variation. The implication of this finding with respect to the dipole hypothesis will be discussed later. Leads 14 and 15 (A and E) are of particular interest since they are respectively analogous anatomically to the transverse and sagittal vectorcardiographic leads used by Donzelot and associates.[11] It should be noted that their coefficients of variation are quite large and that their "disturbing coefficients" approach or exceed 100 per cent, characteristics which suggest that these leads are not satisfactory for vectorcardiographic purposes. Substitution of the unipolar network Leads 20 and 19 for Leads 14 and 15, respectively, would improve this precordial reference frame, but such leads would remain significantly inferior to their bipolar counterparts, 2 (or 1) and 7 (or 8), respectively.

In the last group of Table I, Leads 21 and 22 are compared. They are parallel anatomically. Their mean directions are not too dissimilar electrically, the angular deviation between them being only 8 degrees. Their difference in mean magnitude is almost seven fold due to the fact that points A and E are close to the dipole cluster and points M and I are relatively distant from it. However, their coefficients of variation are practically identical and inordinately large for vectorcardiographic purposes. This serves to illustrate the fact that

the heart will not necessarily function as a satisfactory fixed equivalent dipole with respect to a lead merely because the electrodes of the latter are located in relatively remote positions.

In Fig. 1,*B* the data listed in columns $\bar{x}$, $\bar{z}$, and $\bar{l}$ of Table I are presented graphically by plotting the mean x and z potentials of points A through P, as well as those of certain networks of these points, in image space. It should be emphasized that, in constructing such a diagram, the cluster of seventy-one dipole locations is reduced to a single resultant dipole. Such a manipulation would be justified only for leads whose coefficients of variation approach zero. Nevertheless, it is of interest to compare such a construction with the image loop of dipole location 13, found by Frank to conform most closely to the electrical center of the heart of his experimental subject on the basis of QRS cancellation patterns[4] (see Fig. 5 of Frank's publication[4]).

DISCUSSION

Although the factor of tissue heterogeneity is not taken into account, the data which Frank's publication has made available are superior, for investigations of the type herein reported, to those previously calculated for a circular homogeneous lamina. The use of Frank's experimental results eliminates the objection to the simple but unrealistic boundary condition assumed in the previous paper.[3] The objection may be legitimately raised that the present study, like the previous one, is limited to a two-dimensional approach. However, it should be reiterated, as Frank has already pointed out,[4] that the results which he obtained with the single plane of his three-dimensional torso model would vary from those which would be obtained if his experiments had been performed with a two-dimensional cross-sectional model. Thus, the use of Frank's data in the present study, although limited to the transverse plane, represents a more realistic approach to these problems than that provided by the use of either fluid mappers[12] or Teledeltos paper.[13]

Evidence has accumulated to suggest that, in the majority of instances, the normal heart functions as a single stationary dipole with respect to body surface leads for the duration of QRS.[14-17] Except in the case of bundle branch block, the abnormal heart likewise usually behaves like a dipole during the inscription of QRS.[17,18] The dipole properties of the heart during the inscription of P and T have been less extensively studied. It would seem likely, and there is some published evidence to suggest[17,19] that the single dipole theory is as valid for these waves as it is for the QRS complex. However, the available evidence indicates that the dipole center of the heart often changes its position significantly during the time intervals existing between the recording of these waves.[16,19] Such findings are in accordance with the obvious facts that the atria and ventricles occupy different anatomic positions and that the ventricles change in their location between the inscription of QRS and T as the result of mechanical systole. There is evidence to suggest that relatively small migrations of the "electrical center" of the heart profoundly influence electrocardiographic deflections.[4]

As suggested by theoretic calculations,[20] the explanation for the dipolelike activity of the heart during the inscription of QRS must be intimately related

to a partial cancellation of oppositely directed double-layer forces. This cancellation apparently occurs not only in normal individuals but also in patients with various electrocardiographic abnormalities excluding some cases of asynchronous ventricular activation. If simultaneously occurring cardiac electromotive forces were randomly directed, the relatively large coefficients of variation of certain leads listed in Table I would exclude the possibility of a fixed dipole representation of the heart during successive instants of the QRS interval. The coefficients of variation listed in Table I also provide a possible explanation for the finding of

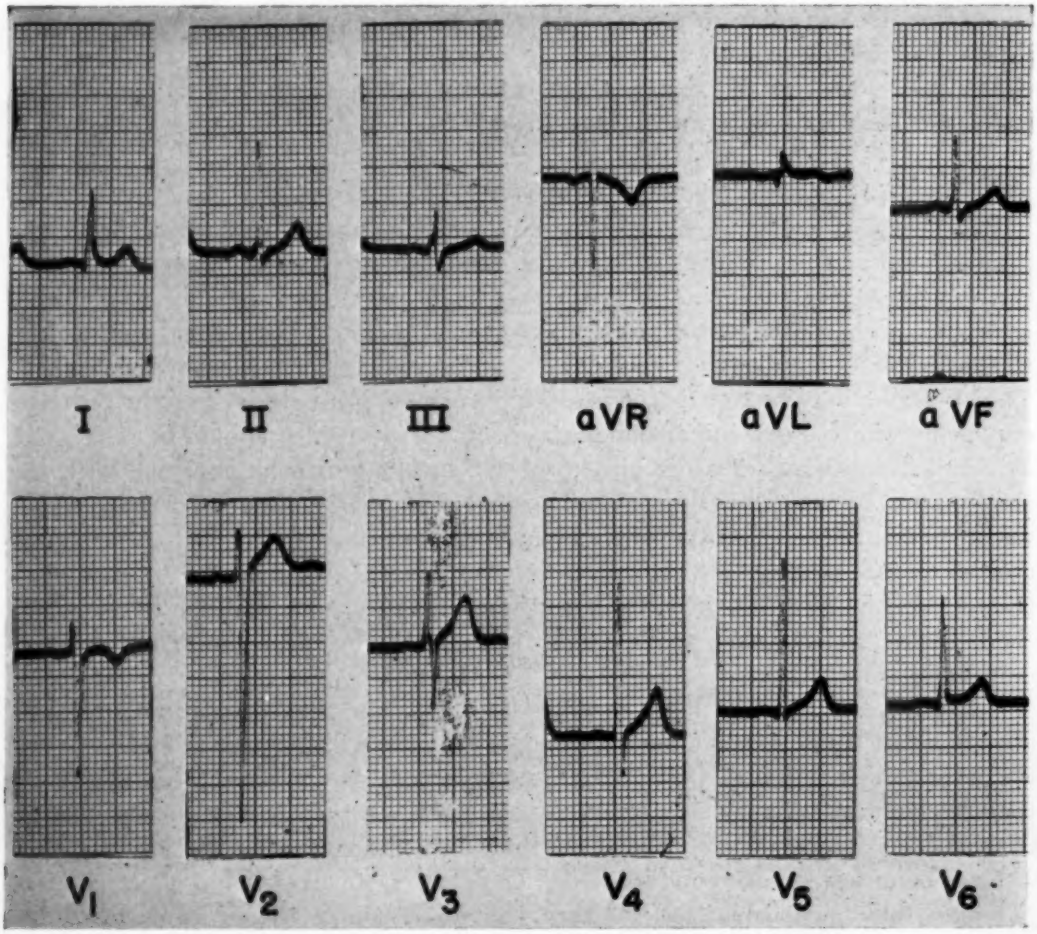

Fig. 2.—Electrocardiogram of subject whose vectorcardiographic leads are illustrated in Fig. 3.

Simonson and associates[18] that the regional distribution of good or poor cancellations over the surface of the body does not show any selective pattern. One might anticipate poor cancellations to involve the use of precordial electrodes. However, as already pointed out under "Results," the coefficient of variation of a lead frequently does not correlate with the relative distance of its electrode attachments from the heart.

If spatial vectorcardiography is to be a relatively exact technique, the hypothesis of a fixed equivalent dipole is not entirely satisfactory since it frequently does not maintain its validity during all phases of the cardiac cycle, nor in all

types of electrocardiographic abnormality including bundle branch block and other forms of aberrant ventricular conduction. It is this fact, based on personal observation[19] as well as a review of published investigations,[2] which has stimulated the approach described in the present and previous communications.[3] It would seem likely that leads designed to have a maximal degree of lead vector uniformity for randomly directed electromotive forces would be less influenced by migration of the "electrical center" of the heart during the cardiac cycle than leads possessing a larger coefficient of variation. In the previous paper,[3] to which the reader is referred for details, a vectorcardiographic lead system, based on this concept, was suggested for further evaluation. An example of the transverse, longitudinal, and sagittal leads of this proposed frame, recorded with stainless steel foil electrodes from an individual with a normal electrocardiogram (see Fig. 2), is illustrated in Fig. 3. The corresponding leads of the tetrahedral and cube systems are also shown for comparison. All leads illustrated were recorded at the identical standardization of 1 mv. = 1 cm. deflection. The relative standardizing factors for each lead system are given beneath the illustrations. The tentative suggestion that equal standardization be used for the three leads of the proposed frame is based on the fact that, in the present study, the mean magnitudes of the x component of Lead 1 and the z component of Lead 8 in Table I are similar. Moreover, these values are not greatly different from a value of 17.6 mv. for the y component of the longitudinal lead between the neck and left leg, based on other data[6,21] published by Frank for a single dipole location.* Equal standardizing factors are assigned to the cube in accordance with the practice of Grishman and Scherlis.[8] The standardizing factors for the equilateral and isosceles tetrahedrons are those based on the assumed geometric forms of these frames.[22] Factors for standardizing the leads of the tetrahedron, based on the recommendations of Frank from his studies of a single dipole in a torso model,[6] are also included. The reader must adjust the size of the deflections of Leads aV_F and V_B in accordance with the standardizing factors of the respective form of the tetrahedron under consideration. (It should be emphasized that standardizing factors of unity do not presume equality of magnitude between leads of different systems.) Fig. 3 illustrates the usual finding that differences in lead contour are most striking in the case of the sagittal component.

In the present study comparison of Leads 1 and 2 and of Leads 7 and 8, Table I, confirms the conclusions previously drawn[3] that, for the transverse and sagittal leads of the proposed lead system, the size of the electrodes located on the posterior and right lateral aspects of the chest is not critical. In fact, it would appear that small electrodes of a size more convenient than originally suggested could be placed in these regions without sacrificing lead vector uniformity. Moreover, since the contribution of these sites to the deflections of their respective leads is relatively small, the accuracy of electrode placement is not critical. The large electrodes located at ventricular level on the anterior and left lateral aspects of the chest may be approximately square and may be centered over regions extending from point G to just medial of point C and from

*From considerations discussed previously,[3] this lead probably possesses relatively uniform lead vectors, which diminishes the error involved in the assumption of a fixed equivalent dipole.

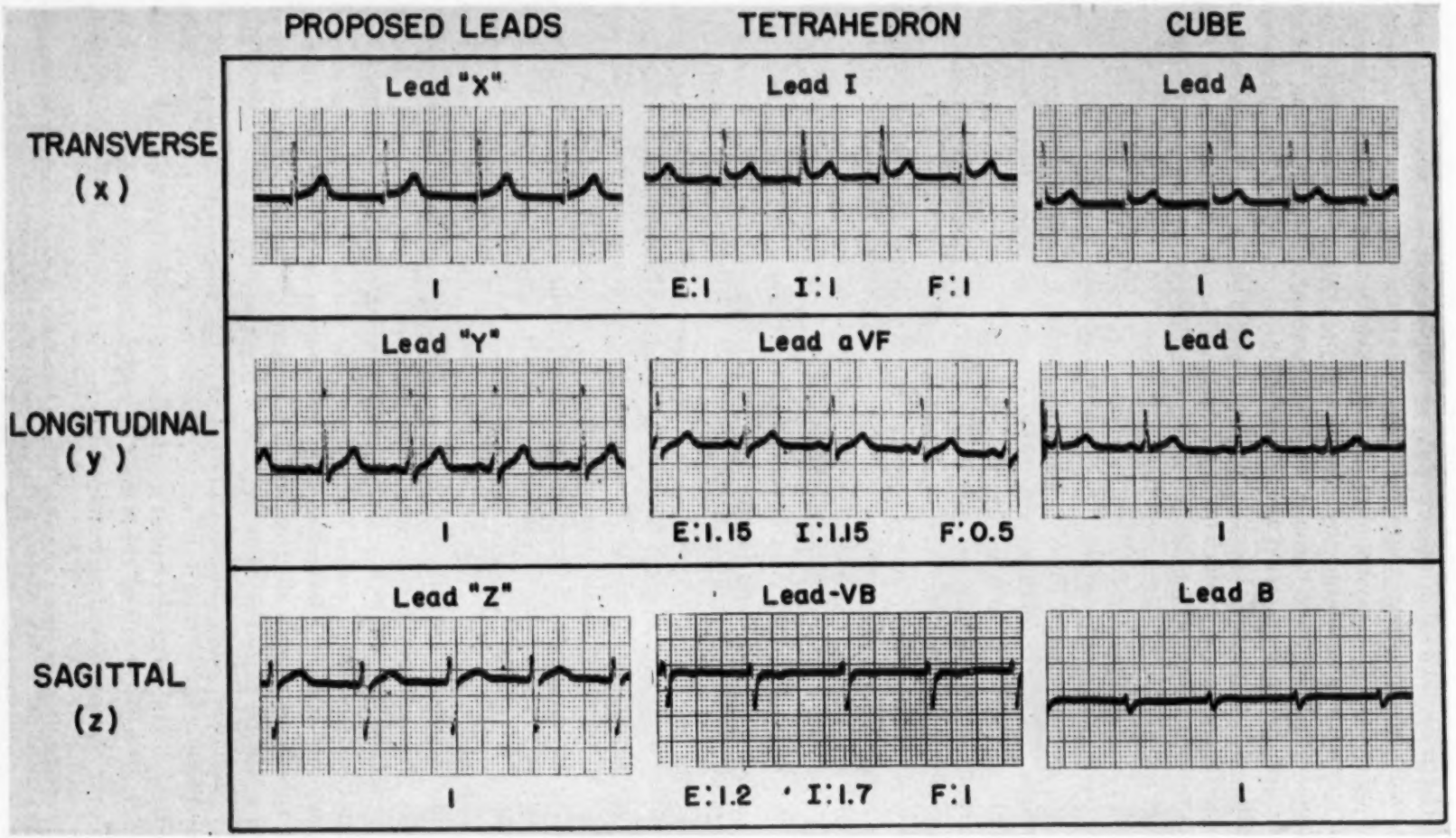

Fig. 3.—The transverse, longitudinal, and sagittal leads of the tetrahedral and cube reference frames, as well as of the proposed vectorcardiographic lead system, were recorded at the same galvanometer sensitivity (1 mv. = 1 cm.). The tetrahedron may take an equilateral (*E*) or isosceles (*I*) form, or a form (*F*) suggested by Frank,[6] depending upon the standardizing factors chosen. See text for a discussion of the standardizing factors, listed under each lead.

point Q to just lateral of point C, respectively (see Fig. 1,*A*). These electrodes must, of course, not be in contact, and, if stainless steel foil is used, inadvertant contact through conducting paste may be prevented by sealing the appropriate edge of each electrode to the skin with a narrow strip of Scotch tape. In the author's experience, stainless steel foil[23] is satisfactory, but other electrode material* might be tried.[24]

The vectorcardiographic reference frame suggested in the previous paper[3] and modified herein, remains a tentative proposal, subject to future evaluation. The present study, representing one facet of this total evaluation, confirms the general conclusions drawn previously from less satisfactory data.

SUMMARY AND CONCLUSIONS

Data, published by Frank for multiple dipole locations on a plane of his torso model, have been subjected to statistical analysis to investigate various leads for use in vectorcardiography from the standpoint of lead vector uniformity. This analysis, which eliminates the objection to the unrealistic boundary assumption made in a previous similar study, confirms, in general, the conclusions drawn from the latter. The most pertinent of these conclusions are:

1. Leads recording the difference in potential between two networks of points, or between a network of points and a single point, can be so designed that their lead vector uniformity is greatly superior to that of any similar lead recording the difference in potential between two single points.
2. Electrode proximity to the heart is not the most important factor which determines the degree of lead vector uniformity of a lead. The latter characteristic is dependent, to a much greater extent, upon the design of the lead.
3. It is likely that a reference frame which utilizes large electrodes for certain of its leads, as described in the previous publication and modified in the present one, is superior to those currently in use in spatial vectorcardiography. This frame appears to be practical for vectorcardiographic recording and its characteristics deserve further evaluation.

SUMMARIO IN INTERLINGUA

Datos publicate per Frank in re le locationes de multiple dipolos in un plano de su modello del torso esseva subjicite a un analyse statistic, e le sequente conclusiones esseva obtenite:

1. Derivationes que registra le differentia in potential inter duo retes de punctos, o inter un rete de punctos e un sol puncto, pote esser construite de maniera que lor uniformitate vectorial es multo superior a illo de omne altere simile derivation que registra le differentia in potential inter duo punctos.
2. Le proximitate del electrodos al corde non es le plus importante inter le factores que determina le grado de uniformitate vectorial de un derivation. Iste characteristica depende multo plus del construction de un date derivation.

*The author has recently found that fine pore synthetic sponge, moistened with a concentrated solution of sodium chloride, is an ideal substance for constructing flexible electrodes to conform to the body contour.

3. Il es probabile que un quadro de referentia que utilisa grande electrodos pro certes de su derivationes es superior, del puncto de vista de uniformitate vectorial, a illos currentemente empleate in le vectocardiographia spatial.

I wish to express my appreciation to Miss Daphne Anderson and Mr. Harold Perlman for their aid in performing the calculations.

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LOCATION OF THE ELECTRICAL CENTER OF VENTRICULAR REPOLARIZATION

PAUL H. LANGNER, JR., M.D., AND SAMUEL R. MOORE, M.D.

PHILADELPHIA, PA.

IT IS the purpose of this paper to present our experience with a method for T-wave mirror pattern cancellation that determines the degree of dipolarity and the location of the electrical center of ventricular repolarization. The method employed in this study was developed by Frank[1] and has been used previously for mirror pattern cancellation of the QRS complex.[2,3] This technique permits geometric matching of data obtained by cancellation of mirror patterns in the human subject to a transverse image locus* of a three-dimensional human torso model.[2,4] Image loci vary considerably in contour and relative size depending upon the degree of dipole eccentricity. Each transverse image locus represents the distribution of potential on the model surface resulting from a particular dipole location. Therefore, the closest fit of human cancellation data to a particular image locus defines an electrical heart center in the subject equivalent to a dipole location in the model.

In the course of performing QRS cancellations it has been noted by Frank,[2] Schmitt and his associates,[5] and ourselves[3] that T waves may or may not cancel with the same pair of electrodes and potentiometer settings that result in QRS cancellation. This fact indicates that electrical centers of ventricular depolarization and repolarization in the same individual are in different anatomic locations. Present methods in vectorcardiography ignore this completely. Because location of the electrical centers is important, it seemed useful to determine the comparative anatomic location of these electrical centers in the same subject. Previous studies[3] indicate that equivalent dipole locations of ventricular depolarization in a group of normal individuals lie in a region near the anatomic center of the ventricles. It was found in the present study of two individuals that the electrical center for T-wave activity was substantially anterior to the QRS center in one and nearly the same as the QRS in the other.

METHOD AND MATERIALS

Two normal men, whose equivalent dipole locations for the QRS had previously been determined, were selected for study. The cancellation method described by Frank[1,2] was followed in principle. A modification in the recording technique was necessary because of the relatively low amplitude of the T wave compared to the QRS. When attempting to observe amplified residuals of

From the Medical Department of the Provident Mutual Life Insurance Company of Philadelphia.
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*The transverse image locus is that line in image space which corresponds to the anatomic line around the chest at the transverse level of the electrical heart center.

T-wave cancellation on the visocardiette the accompanying uncanceled QRS was usually so large that the writing arm forcibly impinged on the metal sides at the edge of the recording paper. This caused a rebound phenomenon which significantly distorted S-T segments and T waves. Therefore, mirror patterns and cancellation residuals were observed on a cathode ray oscilloscope with a long persistent phosphor using a synchronized driven sweep. A preamplifier, specially designed by Frank for his cancellation procedure, was fed into a second high gain Sanborn preamplifier, and this in turn into the cathode ray oscilloscope. When the smallest residual resulting from cancellation of any given pair of mirror patterns had been visually selected the input was fed into a DuMont CRO type 322. For each cancellation the mirror patterns and residual potentials with corresponding standardization for each signal were recorded by photographing the unswept vertical deflection of the beam with a Westinghouse camera at a paper speed of 12 cm. per second. The maximum amplification which could be utilized was obtained. With the apparatus used, amplification of 1.0 mv. = 1 meter was possible, but the degree of amplification was limited by base line drift, muscle tremor, electrical interference, and cathode ray tube width of five inches. Residual potentials were usually recorded with a standardization of 0.2 mv. = 30 to 70 mm. The problem of muscle tremor at high amplification was minimized by insertion of a 120 cycle band-rejection filter after ascertaining that this did not significantly alter the character of the T waves. It has been found in a study of over 300 individuals using equipment with an amplitude response extending to 5,000 cycles per second that, unlike the QRS, the T wave has no high frequency components.[6] Therefore, the use of this rejection filter seemed quite justified. Base line drift, a problem particularly at high amplification, was minimized by recording cancellation residuals with the subject holding his breath at the end of a quiet expiration. This had the additional advantage of reducing to some extent dipole respiratory shift. Another source of difficulty which we anticipated but did not encounter to any significant degree in our subjects was the possible variation in the amplitude and configuration of the T waves which is seen from time to time in clinical electrocardiography.

T-wave cancellation differed from QRS cancellation in another important respect. For the QRS, small changes in electrode position were sensitively reflected in the cancellation residual and it was possible visually to select the smallest QRS cancellation potential. However, in this study we frequently found that the T waves looked alike and cancellation by gross visual inspection appeared excellent over relatively wide anatomic areas around the thorax at heart center level. Hence it was necessary in most areas explored for a mirror pattern to record apparent mirror patterns and residual cancellation potentials at many anatomic points. The cancellation coefficients were then calculated to determine the precise anatomic location of electrode pairs most nearly representative of true mirror patterns. The degree of cancellation was determined by the formula of Schmitt and associates.[5]

In the two individuals studied the electrical heart center level had been previously determined during location of the QRS center. This same level was utilized for the T study. In several preliminary explorations in each individual

it was found that residual cancellation potentials determined two inches above and below electrical heart center level were greater than at heart center level. Because of the excessive amount of time necessary for determination of the T center, the time was shortened somewhat by determining cancellations only in horizontal angle at a single level. It has been our experience in studying QRS mirror patterns that once the heart level had been determined search at this level only was sufficient to find the correct anatomic location of electrodes for recording mirror patterns.

The method of recording was time consuming and necessitated meticulous attention to detail requiring an average time for each cancellation of from two to three hours with a total time of eighteen to twenty-two hours for each subject. Several points for each subject were repeated two or three times to confirm the reproducibility of cancellation points found. In order to check the validity of the cancellation determinations in each subject, before plotting data geometrically, two cancellations, one from front to back and one from side to side, were repeated and completed at one sitting. Locations of electrodes and potentiometer settings did not differ significantly from previous results.

When six to eight cancellations had been determined for each subject, locations of electrodes for various cancellations and settings of potentiometers joining electrodes were plotted geometrically on various transverse image loci. The image locus providing the smallest cluster of points representing potentiometer settings established the equivalent dipole location for ventricular repolarization in that subject.

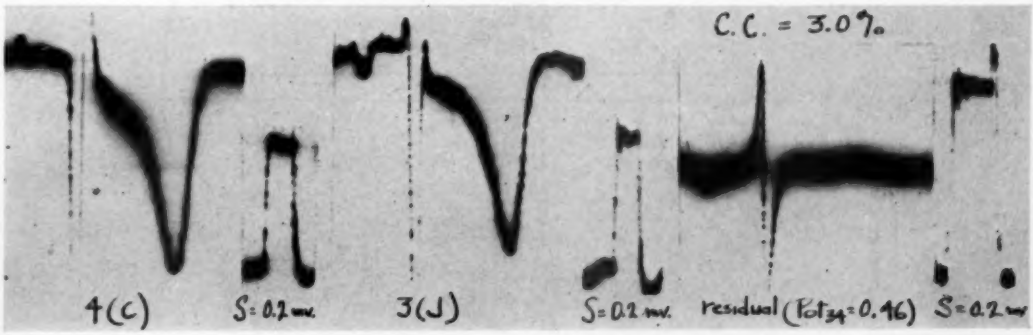

Fig. 1.—Sample record of a cancellation from subject H.H. From left to right are shown T-wave mirror patterns recorded by electrode 4 at *C*, 3 at *J*, and residual cancellation potential, with corresponding standardization of 0.2 mv. to the right of each complex. This illustration has been photographically reduced. The standardization voltages in the original size are as follows: For 4(*C*), 0.2 mv.=4.5 cm.; for 3 (*J*), 0.2 mv.=4.6 cm.; and for residual, 0.2 mv.=6.7 cm. *Pot*$_{34}$ indicates fractional setting of potentiometer connecting electrodes 3 and 4. Cancellation coefficient (*C.C.*) is indicated above the record. Polarity of mirror pattern recorded by electrode 3 at *J* has been reversed for convenience of comparison. While T-wave cancellation is excellent, it can be seen that the P and QRS waves are uncanceled.

RESULTS

In two normal subjects the degree of cancellation of T-wave mirror patterns ranged from 91 per cent to 99 per cent. Cancellation coefficients averaged 3.7 per cent. Electrode positions, potentiometer settings, and cancellation coefficients are summarized in Table I. Fig. 1 illustrates typical cancellation

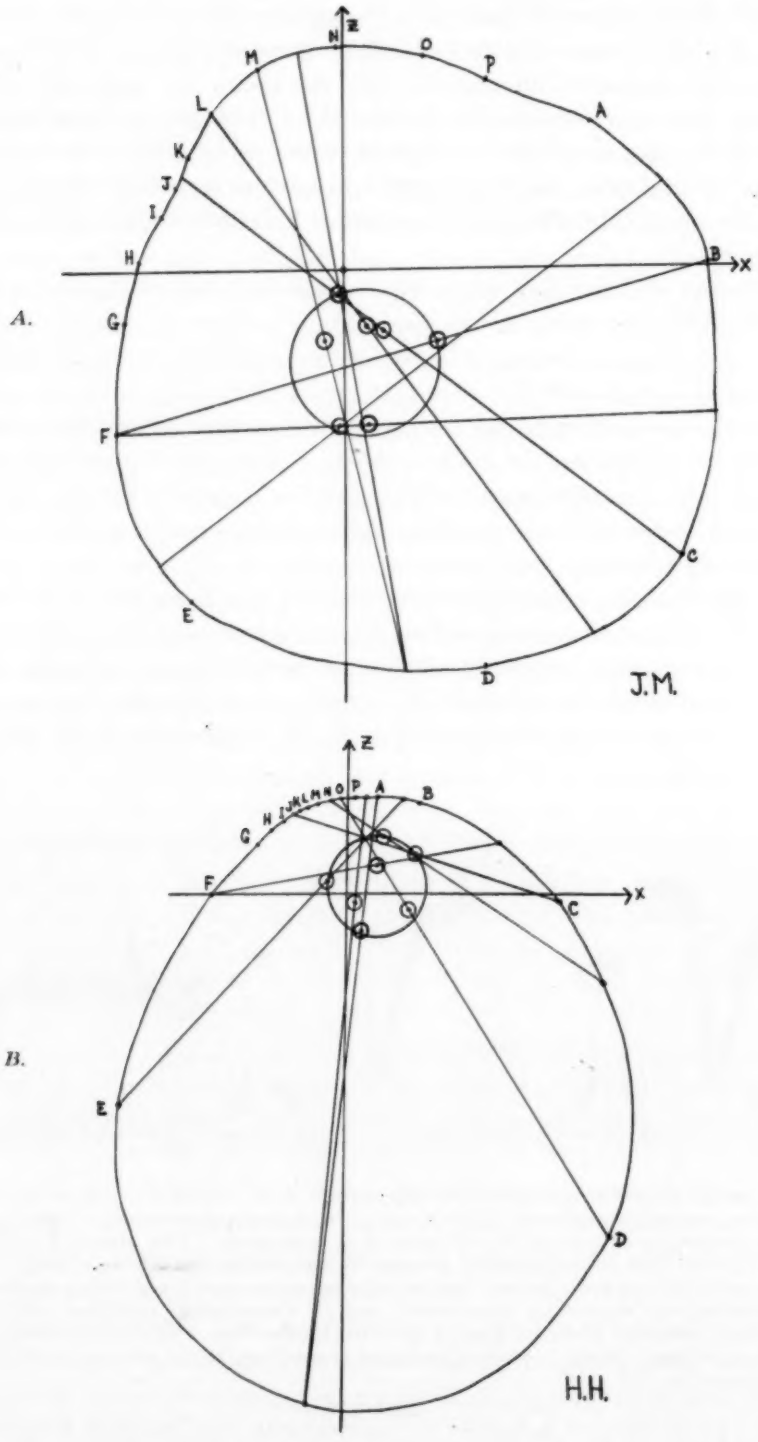

Fig. 2,*A* and *B*.—The transverse image loci for two subjects to which cancellation data fitted most closely. Lines connect reference electrodes and pairs of electrodes recording mirror patterns. Dots on the lines are geometric points representing potentiometer settings. Each cluster of dots is encircled. These image loci produced the tightest cluster of points representing potentiometer settings and were selected as indicating the equivalent dipole locations of repolarization. The image locus for subject J.M. results from anatomic dipole location 22; that for subject H.H. from location 27.

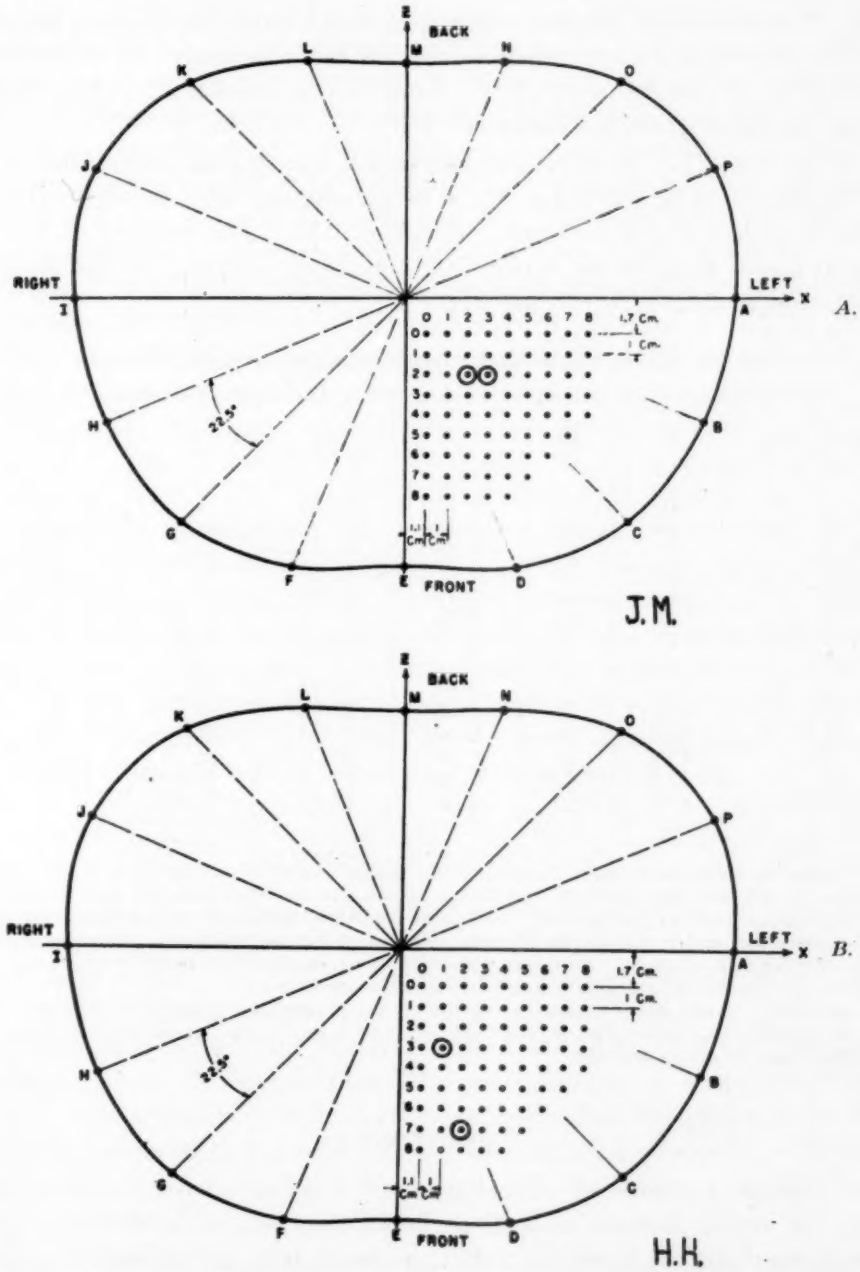

Fig. 3,*A* and *B*.—Anatomic transverse view of the chest. Anatomic equivalent dipole locations for each subject within the heart area. In subject J.M. (*A*) the location for the QRS was 32; that for the T, 22. In subject H.H. (*B*) the location for the QRS was 13; that for the T, 27. These locations are shown on a diagram of the transverse plane through mid-dipole level in the torso model, the postero-anterior dimension of which was 25 cm. and the lateral, 33 cm. More precise location of the equivalent QRS and T dipoles would require expressing each location in terms of the ratio of thoracic dimension of each subject to those of the torso model. The thoracic dimensions of J.M. were 28 cm. (postero-anterior) by 36 cm. (lateral); and of H.H., respectively, 26 cm. by 31 cm.

records. The image loci for each subject to which cancellation data fitted most closely are shown in Fig. 2. In one case (H.H.) the image locus results from dipole location 27; in the other (J.M.) from dipole location 22. (For method of obtaining dipole location see Reference 2.)

Anatomically (Fig. 3) the equivalent dipole location for ventricular depolarization in subject H.H. (location 27) is 4 cm. anterior and 1 cm. to the left of that for ventricular depolarization (location 13). For subject J.M., whose equivalent dipole location for ventricular depolarization was 32, the location for repolarization was 22, 1 cm. to the left.

TABLE I. DATA FROM WHICH DIPOLE LOCATIONS WERE DERIVED

SUBJECT	D.L.	E_1	E_2	P_{1-2}	E_4	E_3	P_{3-4}	C.C.
H.H.	27	D	O	0.75	C.25	N	0.21	2
		D	O	0.75	C	J	0.46	3
		D	O	0.75	E	A.5	0.28	3
		D	O	0.75	D.5	P.5	0.17	3
		D	O	0.75	D.5*	A	0.22	4
		D	O	0.75	F	B.5	0.41	7
		D	O	0.75	F*	B.5	0.41	3
J.M.	22	C.5	L	0.60	D.25	M.5	0.39	3
		C.5	L	0.60	D.25*	M	0.44	3
		C.5	L	0.60	F	B.5	0.58	3
		C.5	L	0.60	F*	B	0.46	5
		C.5	L	0.60	C	J.5	0.40	1
		C.5	L	0.60	E.25	A.5	0.65	9

D.L. indicates equivalent dipole location in the human torso model for each subject; E_1 and E_2 are positions of reference electrodes; E_3 and E_4 are positions of electrode pairs for various cancellations; C.C. is cancellation coefficient in per cent. P_{1-2} is the fractional setting of the potentiometer connecting reference electrodes 1 and 2. P_{3-4} is the fractional setting of the potentiometer connecting pairs of electrodes for various cancellations. Numbers following letter designations indicate fractional distances between lettered angles; for example, B.5 is halfway between B and C.

*In each subject, two cancellations were repeated at one sitting. While it is very difficult or impossible to reproduce a cancellation exactly, the repeated results were not sufficiently different to influence final choice of dipole location.

DISCUSSION

The excellent degree of cancellation of T-wave mirror patterns indicates that normal repolarization, as well as depolarization, is dipolar in nature and further strengthens the hypothesis that the heart acts approximately as a dipole. The P waves did not cancel when the T waves canceled, as noted previously, indicating a different location for the electrical center of auricular depolarization.

In one subject (H.H.) whose equivalent dipole location for ventricular repolarization was significantly anterior to that for depolarization, the cluster of data for the image locus, representing dipole location 27, was definitely smaller than for all other image loci representing adjacent dipole positions, so that the result was well defined. However, in subject J.M., while the image locus for dipole location 22 yielded the smallest cluster, several adjacent image loci resulted in clusters which were not much larger. It therefore seems reasonable to

assume that within limits of error the equivalent dipole location in this case lies somewhere within a 1 cm. radius from location 22. In this subject the equivalent dipole locations for the QRS and T waves were not significantly different. However, in the other subject the equivalent dipole locations differed anatomically by approximately 4 cm. If this amount of separation is found frequently it would seem necessary to allow for this in ultimate systems of precise quantitative vectorcardiography. Our findings suggest that a system of vectorcardiography which is insensitive to variations in dipole location, such as the SVEC III of Schmitt and Simonson[7] or the precordial system of Frank,[8] is essential in view of the possible differences in location of QRS and T centers. It will be necessary to further define in normal and abnormal hearts the range of electrical center locations for ventricular repolarization before drawing final conclusions.

SUMMARY

A method for determining the equivalent dipole locations of ventricular repolarization is described which utilizes a precise cancellation procedure described by Frank, with modification of the recording apparatus. Two individuals, whose equivalent dipole location for ventricular depolarization had previously been determined, were studied. It is concluded that repolarization is dipolar in nature. In one individual the equivalent dipole location for ventricular repolarization was approximately 4 cm. distant from that for depolarization, but in the other the distance between these two centers was only 1 cm.

SUMMARIO IN INTERLINGUA

Es describite un methodo pro determinar le equivalente locationes dipolic de repolarisation ventricular. Iste methodo utilisa le precise procedimento de cancellation describite per Frank, con un modificate apparato de registration. Esseva studiate duo individuos pro le quales le equivalente locationes dipolic pro dispolarisation ventricular habeva essite determinate. Il es concludite que repolarisation es dipolic per natura. In un individuo le equivalente location dipolic pro repolarisation ventricular esseva approximativemente 4 cm distante ab illo del dispolarisation, sed in le altere le distantia inter iste duo centros esseva solmente 1 cm.

We wish to express our appreciation for the assistance of Ernest Frank, Ph.D., who made invaluable suggestions during the course of this study and critically reviewed the final manuscript.

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THE "APERIODIC" BALLISTOCARDIOGRAM AS A FUNCTION OF AGE

C. R. HONIG, M.D., AND S. M. TENNEY, M.D.

ROCHESTER, N. Y.

INTRODUCTION

A SENSITIVE, quantitative, painless technique for analysis of mechanical heart action would be ideal for clinical research and screening for asymptomatic heart disease. The need for such a method has stimulated numerous investigations of the normal ballistocardiogram all of which suggest the value of the method if physical and biologic factors were adequately controlled.[1-4]

Recent studies of the body as an oscillator have demonstrated that the tissues determine the vibration properties of the body-platform system and introduce the major distortion.[5,6] On the basis of these investigations several new ballistocardiographs have been designed with mechanical constants selected to eliminate tissue distortion.[6-8] The output of all these "aperiodic" instruments may be cautiously interpreted in terms of specific physiologic events and calibrated in absolute units of force. Using similar apparatus designed for animals the qualitative relationships between the ballistocardiogram, cardiac motion, and blood flow have been determined, and the biologic factors influencing the record have been analyzed.

This study defines the normal human "aperiodic" ballistocardiogram as a function of age in the light of current physical and physiologic understanding.

METHODS

A. *Instrumentation.*—The ballistocardiograph is a modification of that described by Wittern.[7] It consists of an ovoid frame of aluminum extrusion covered by a spot-welded sheet aluminum "sandwich," the top layer smooth, the bottom corrugated for added rigidity. Though it weighs but 10.5 pounds it supports over 500 pounds without objectionable torsion or bend. This platform is suspended from the ceiling to a natural frequency of 0.3 c. p. s. Single piano wire strands are attached to the main cross member at shoulder position; the foot end of the longitudinal member is fixed to the apex of a wire "V," the divergent limbs of which are 2 meters apart at the ceiling. Motion is thus restricted to longitudinal translations and lateral rotations about the apex of the "V."

From the Department of Medicine of the University of Rochester School of Medicine and Dentistry, Rochester, N. Y.

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Since displacements are on the order of 0.01 mm., lateral movements may be treated as translations. A single appropriately placed piston and oil cylinder damps both longitudinal and lateral motion. Though damping is somewhat weight dependent, no attempt is made to adjust it for body weight since cardiac and calibration forces are altered equally, and wave form is unaffected.

Longitudinal and lateral acceleration is measured directly with crystal accelerometers* secured to the frame at approximately heart position. Though the frequency response of the body-platform system is flat from 0.4 to 35 c. p. s., the band 0.5 to 25 c. p. s. is selected with a band pass filter.[10] Accelerometer signals are preamplified, filtered, further amplified, and recorded on a Sanborn polyoscillograph. Records of body momentum are occasionally useful and may be obtained by electrical integration.

The new apparatus differs from the original in three important respects: (1) It is suspended to a natural frequency of 0.3 c. p. s., (2) It may move with two degrees of freedom, and (3) It is half as heavy.

B. *Calibration.*—The displacement calibration described by Starr[2] cannot be applied to moving forces; these require a known dynamic force the frequency of which is within the range of linear response for the recording system. A sinusoidal calibration force is therefore provided by a motor-driven† mass-loaded pendulum fixed to the platform at approximately heart position, and arranged to oscillate in resonance at exactly 2 c. p. s. A pivot permits application of force in, or 90 degrees to the long axis of the platform. At pendulum frequency tissue compliance is so small that calibration force acts simultaneously on platform and "total body mass."[7] Because the first and second harmonics of the ballistic frequency spectrum are weak[10] one may virtually "switch off" cardiac force during calibration by attenuating frequency response to 2.5 c. p. s. Though this decreases calibration amplitude sufficiently to necessitate a correction factor, it ensures maximal attenuation of the ballistocardiogram. When the 2.5 cycle ballistic remnant is large, (as in the hyperkinetic states), calibration is best accomplished by loading the platform with the patient's weight in ballast. This should not be necessary, however, for normal subjects.

C. *Recording Procedure and Method of Measurement.*—Patients were fixed to the platform by longitudinal and lateral shoulder restraints and an adjustable foot plate. After a fifteen-minute rest period in the postabsorptive state longitudinal and lateral force were recorded simultaneously with the electrocardiogram and pneumogram at paper speed 50 mm. per second throughout at least four respiratory cycles.

All records were categorized by one of us (C.R.H.) as normal, borderline, or abnormal on the basis of qualitative criteria gained by experience. Quantitation was possible in every subject and was accomplished by comparing calibra-

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*Crystal accelerometers may be obtained from Mr. John Frank, 1301 Shawnee, Yellow Springs, Ohio.

†A suitable motor and reduction gear weighing 12 ounces is available from Globe Industries, Inc., Dayton, Ohio.

tion amplitude with the average of all peak-to-peak values for the wave of interest during one complete respiratory cycle.

D. *Composition of Normal Series.*—The records of thirty-nine males and thirty-four females ranging in age from 2½ to 87 years constitute the material for this report. All children were family members or neighbors of the authors, familiar with the apparatus, and free of anxiety. Only subjects over 18, however, were included in the statistical analysis. With few exceptions subjects between 18 and 70 were actively working as students, laboratory personnel, or non-professional employees of the Strong Memorial or Rochester Municipal hospitals. Those over 70 were active, ambulatory, custodial patients of the Monroe County Home. Clinical charts were available for all patients and hospital employees; some of the latter had been followed in the outpatient clinics for as long as ten years. All adults had chest x-ray and complete physical examination by an independent observer.

Records were made repeatedly on laboratory personnel and four elderly hospital employees.

RESULTS

A. *Morphology and Timing.*—Normal longitudinal and lateral force ballistocardiograms in youth and senescence are illustrated in Fig. 1. They consist of three major waves, the result of independent forces following closely in time. The first is related to atrial contraction, atrioventricular blood flow, and isometric contraction. It begins 0.08 to 0.10 second after the onset of auricular depolarization, and exhibits its second and largest peak 0.08 to 0.12 second after the onset of ventricular depolarization. The second wave follows ventricular depolarization by 0.18 to 0.24 second and dominates the record. It is related to acceleration of a central arterial volume; cardiac motion does not contribute significantly. The third wave is a summated complex of diastolic events including venous decelerations, oscillations generated by the aortic standing wave, and perhaps diastolic cardiac motion.[11]

With the subject on his side force may be studied in the sagittal plane. Anteroposterior ballistocardiograms are dominated by waves one and three, probably because cardiac motion is chiefly exhibited in the sagittal plane with the body in this position. Wave two is usually the smallest oscillation, and seldom exceeds one-third its amplitude in the simultaneously recorded longitudinal ballistocardiogram.

Each subject tested repeatedly exhibited a distinctive and highly reproducible pattern. The record of C.R.H., for example, has remained constant over a three-year period. Although morphologic differences were common within the group, the precise shape of the ballistocardiogram appeared to be a stabile individual characteristic.

B. *Morphologic Changes With Age.*—Longitudinal and lateral ballistocardiograms are similar, and corresponding deflections may be readily identified. In subjects under 35 lateral records may be somewhat complex, with diastolic vibrations similar to those of anteroposterior ballistocardiograms. In middle

life longitudinal and lateral records are usually indistinguishable, while beyond age 50 lateral wave form definition improves and longitudinal records take on the appearance of the lateral trace in youth. These age differences parallel the change in direction of the frontal plane force vector.

C. *Quantitative Analysis.*—Scatter of the raw data is considerably improved by correcting for body size, but not by separate consideration of the sexes. It has been our experience that total force parallels basal metabolic rate, which in turn is related to body surface area. Results are therefore expressed in terms of dynes per square meter body surface area, thus standardizing the factor of shape as well as size.

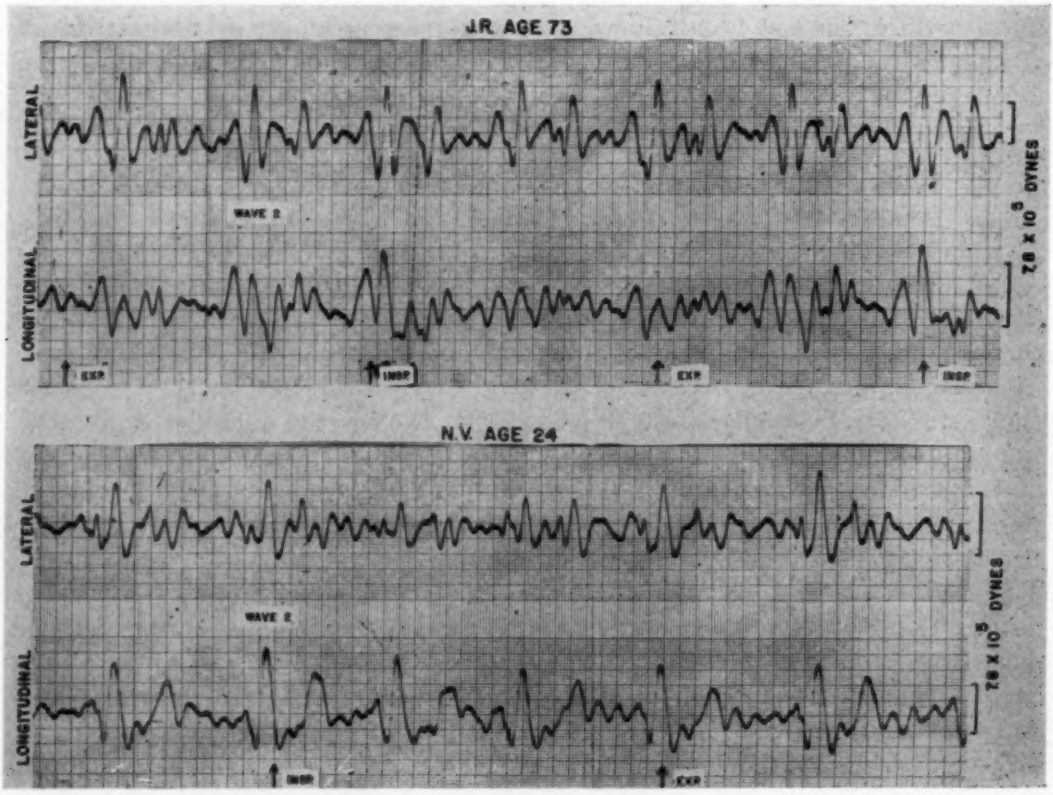

Fig. 1.—The normal "aperiodic" ballistocardiogram in youth and senescence. Discussion in text.

Only wave two is quantitated, for it alone appears to represent a single physiologic process, namely systolic ejection.[11] Longitudinal headward and lateral right-left forces are most informative, though footward force is occasionally useful. Fig. 2,*A*, *B*, and *C* presents normal values for these forces as a function of age. The range indicated as two standard deviations pertains only to the enclosed values. Note that longitudinal force decreases slightly through childhood, remains constant between 18 and 40, then decreases abruptly. Lateral force on the other hand is relatively small in children and young adults, but increases markedly beyond age 40.

Fig. 2,*G* demonstrates that the decrease in longitudinal force can be accounted for by increase in lateral force, their sum as well as their frontal plane resultant remaining virtually constant throughout adult life. Certain discrepancies, however, suggest that three-dimensional analysis would improve the data, particularly in the elderly. When a young subject is rotated 180 degrees about his long axis (back down to face down), longitudinal amplitude decreases, lateral deflections are inverted and increased, but the increase is often insufficient to maintain the frontal plane resultant constant. Since anteroposterior ejection force is small

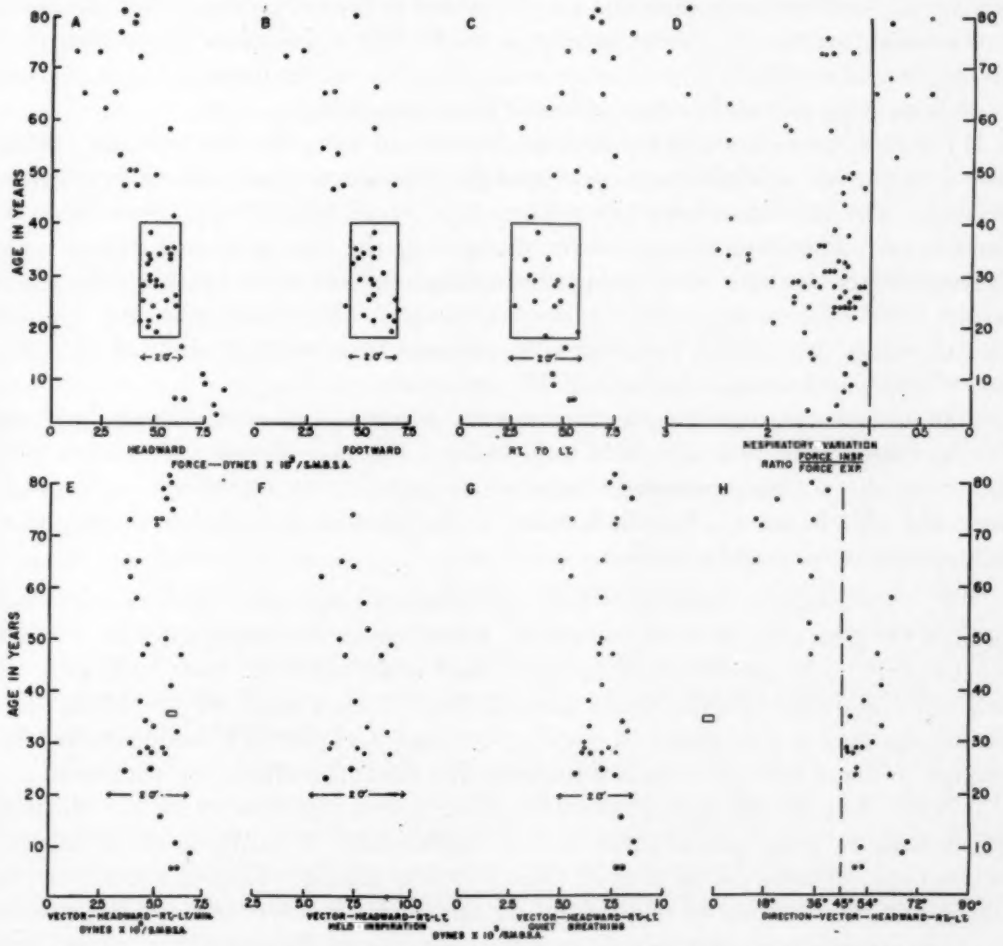

Fig. 2.—Cardiac force and respiratory variation as a function of age. Discussion in text.

in youth the reproducibility of longitudinal force between 18 and 40 may be due to its virtually complete exhibition in the frontal plane. In the same age group, the scatter of normal values, discrepancies with rotation, and pecularities of lateral wave form suggest that a large and variable component of lateral force is outside the frontal plane. The reverse situation obtains in the elederly. Until changes in force distribution between frontal, sagittal, and horizontal planes are more thoroughly investigated low values for frontal plane force in subjects over 60 should be interpreted with caution.

It is important to note that the standard deviation for repeated measurements of frontal plane force in a single subject is less than one-half that for the group, emphasizing the reproducibility of the ballistocardiogram for the individual.

Fig. 2,*H* quantitatively displays the change in direction of frontal plane force with age. Direction is expressed as the angle whose tangent is defined by the vector ratio: longitudinal/lateral force. Angles greater than 45 degrees indicate longitudinal force in excess of lateral. Note that the frontal plane vector of every subject under 40 exceeds 45 degrees with respect to the transverse axis of the body. Conversely, practically every subject over 40 has a vector oriented less than 45 degrees to the body's transverse axis. Similar results using another method have been reported by Scarborough and his colleagues.[12]

Fig. 2,*E* was obtained by multiplying stroke force by the average cardiac rate over the same respiratory cycle used for measurement of ballistic amplitude. Standard deviation for force per minute is only slightly greater than for force per stroke. The data are useful for evaluating the effects of rate per se as in thyrotoxicosis, and for identifying the normal subject with bradycardia whose stroke force exceeds the arbitrary normal range. The closed square in Fig. 2,*E* and *G* represents such a patient, a 36-year-old man with congenital complete heart block, and ventricular rate of 38 per minute.

In an attempt to minimize the influence of respiration records were analyzed during held inspiration and held expiration. Fig. 2,*F* shows that this greatly increases the scatter, probably because of inability of untrained subjects to keep the glottis open. Breath holding then becomes a Valsalva maneuver of unknown intensity and duration.

C. *Respiratory Variation.*—Fig. 2,*D* presents respiratory variation in longitudinal force as the conventional ratio: force inspiration/force expiration. The scattergram includes twenty-four additional male subjects examined with the original apparatus of Wittern.[7] Careful beat-to-beat analysis of bidirectional recordings over a wide range of respiratory rates and patterns demonstrates that change in force direction cannot account for normal respiratory variation.

Note that all subjects under 40 exhibit a ratio greater than 1, indicating an increase in longitudinal force during inspiration. Two-thirds of all subjects beyond age 50 have ratios greater than 2 or less than 1. Lateral force bears no consistent relationship to respiration at any age. It therefore seems probable that respiratory variation as well as amplitude follows the pattern of lateral force after middle life.

DISCUSSION AND CONCLUSIONS

The results reported above differ sharply from previous investigations of the normal ballistocardiogram, based on unidirectional recording without elimination of tissue resonance. In a conservative, carefully designed study employing a high frequency bed the incidence of abnormal ballistocardiograms in clinically healthy subjects increased from 2 per cent under age 40 to 50 per cent between 50 and 60, and 92 per cent beyond age 70! Only one-third of 155 subjects over 50 had records suitable for measurement, and of these only three

could be found over age 60.[1] The influence of sex and body size has been controversial,[1,2] but no matter how the data have been expressed decrease in force with age has been a uniform finding.[1-4]

In contrast, wave form was adequate for quantitation in all our normal subjects. Although there were no gross abnormalities such as we have observed in overt heart disease, minor deviations from the group pattern were common, particularly in the elderly. In evaluating these changes it is important to realize that wave morphology is dependent upon force direction; this is true during positional change even in young subjects. As age advances the direction of the frontal plane vector changes from a primarily longitudinal to a lateral orientation. The resulting alterations in wave form are often sufficiently characteristic to permit one to predict whether a record is that of a young, middle aged, or elderly subject simply by comparing longitudinal with lateral wave morphology. It is probable that the force vector also changes its orientation in the sagittal and horizontal planes. Finally many factors other than change in force direction are capable of altering wave form. Qualitative criteria are therefore so difficult to construct that we have been reluctant to attribute clinical significance to changes which do not differ grossly from the group pattern. We fully realize that some of our presumably normal subjects have subclinical heart disease, and that the very changes we ignore may be the subtle diagnostic features which separate the sick from the healthy. The technique of long term follow-up used so effectively by Starr[13] must be applied to the "aperiodic" ballistocardiogram, however, before details can be interpreted with confidence.

Some of the difficulties inherent in mass analysis may be circumvented by using the individual as his own diagnostic standard, a technique commonly used in electrocardiography. We have shown that the ballistocardiogram is a highly reproducible individual characteristic, both qualitatively and quantitatively. In a patient suspected of angina, for example, a record might be diagnostic if it represented sudden change for the individual, yet be interpreted as normal if it were an original observation.

Statistical analysis indicates that the output of the cardiac "generator" varies with the size but not the sex of the consumer. Though rate correction does not improve the data for subjects with normal sinus mechanism it is useful for delineating the effects of rate per se. Though a reversed respiratory variation ratio is highly significant in subjects under 40, no clinical importance can be attached to it beyond age 50.

The most striking and important difference between the results of this study and those of previous investigations is illustrated in Fig. 2,*A*, *C*, and *G*. Though longitudinal force decreases progressively with age, lateral force increases sufficiently to maintain the frontal plane resultant at virtually constant magnitude. Ancillary evidence suggests that this relationship would be even more precise were three-dimensional analysis employed.

Constant reaction force throughout adult life does not imply constant cardiac contractility or "strength," for only the kinetic component of heart muscle function can be measured as reaction force. The amplitude of the wave selected for analysis is proportional to the product of stroke mass and stroke

acceleration.[11] Acceleration is dependent not only on the inotropic properties of heart muscle but also upon the vascular impedance, which includes the inertia of the central volume to be accelerated, distensibility of vessels, and frictional resistance.[14] Stroke volume decreases progressively with age at the rate of approximately 1 per cent per year.[15] The inertial component of impedance should decrease with age in proportion to the decrease in stroke volume. Since mean blood pressure does not change significantly the increase in frictional resistance with age is also directly related to the decline in cardiac output.[15] The most important and constant feature of the circulatory aging process is a decrease in distensibility of the central vessels. The probable net change is a decrease in vascular impedance in the elderly, with a consequent increase in the proportion of total cardiac function exhibited as kinetic rather than potential energy. It is this relative increase in kinetic energy which maintains reaction force constant despite decrease in cardiac output and contractility in the aged.

Clinical experience in this and other laboratories has demonstrated the value of the "aperiodic" ballistocardiograph for clinical diagnosis and research.[8] The authors have been disturbed, however, by the increasing tendency to employ simple ballistic systems for routine diagnosis, despite previous evidence indicating the need for caution.[1] This study demonstrates that the effects of normal aging compound the already severe shortcoming of such methods sufficiently to render them useless in the age group of interest. The size and complexity of instrumentation at present required for meaningful ballistocardiography precludes its use as an office procedure.

SUMMARY

1. A modification of the Wittern "aperiodic" ballistocardiograph, capable of quantitative registration of force in 2 degrees of freedom is described in detail.

2. The records of seventy-three normal subjects ranging in age from 2½ to 87 years comprise the material for this report.

A. The wave form of the "aperiodic" ballistocardiogram varies with age and force direction, though the shape of the record for any single individual is a unique and highly reproducible characteristic.

B. Progressive shift of the frontal plane vector toward the transverse axis of the body begins at approximately age 40. Bidirectional recordings are therefore essential in the age group of primary clinical interest.

C. Respiratory variation cannot be explained on the basis of change in force direction. Though reversed respiratory variation is highly significant in subjects under 40, it may be entirely normal beyond age 50.

3. The most important fact elucidated by this study is that reaction force remains constant throughout adult life. The hemodynanic alterations responsible for constant force output despite progressive decrease in stroke volume and contractility are discussed.

4. Though the "aperiodic" ballistocardiogram has proved to be a valuable clinical and investigative technique, the complexity of instrumentation and interpretation precludes its use as a "service" diagnostic procedure in its present state of development.

SUMMARIO IN INTERLINGUA

Es describite un ballistocardiographo "aperiodic" que registra quantitativemente le fortia in duo grados de libertate, e es presentate le resultatos de su application a individuos normal de etates de inter 3 e 87 annos. Le forma del undas varia con le etate e le direction del fortia, ben que le precise configuration del ballistocardiogramma es un reproducibile characteristica individual. Post le etate de 40 annos, le direction del fortia del plano frontal se displacia verso le axe transverse del corpore. Isto resulta in vitiar le valor diagnostic del variation respiratori, e technicas bidirectional de registration deveni essential. Le fortia total de reaction remane constante durante le vita adulte malgrado le diminution de rendimento e contractilitate cardiac. Le factores hemodynamic responsabile pro isto es discutite. Al presente le complexitates de instrumentation e de interpretation non permitte le application del ballistocardiogramma al routinari diagnose clinic.

We are indebted to Mr. Wolf von Wittern who designed the accelerometers and assisted with the modification of the platform. We also wish to thank Mr. Carl Mosher, Assistant Administrator, Strong Memorial Hospital, Mr. William B. Woods, Administrator, Rochester Municipal Hospital, and Dr. Eric S. Green, Medical Director, Monroe County Hospital, for their cooperation in supplying subjects for this study.

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THE BALLISTOCARDIOGRAM IN CONGENITAL HEART DISEASE

EPHRAIM DONOSO, M.D.,* LEON PORDY, M.D., YUSUF Z. YUCEOGLU, M.D.,
JAMES B. MINOR, M.D., KENNETH CHESKY, M.D., AND
SALOMAO S. AMRAM, M.D.

NEW YORK, N. Y.

INTRODUCTION

THE studies reported in the literature on the ballistocardiographic findings associated with congenital cardiac anomalies have been relatively few.[1-7] Brown and associates,[3] Nickerson and colleagues,[4] and others[5-7] have reported an abnormal K wave in the ballistocardiograms of patients with coarctation of the aorta and have described the return to normal following surgical resection. Reissmann and associates[6] have reported that the I wave is increased in both depth and duration in coarctation of the aorta. Similar changes in the K wave have been found in other disease states[8-12] and even in normal individuals under conditions of physical stress.[8]

No consistent ballistocardiographic pattern has been found in patients with patent ductus arteriosus. Rager and his group[13] found that the H, I, and L waves were increased in amplitude, the latter being followed by "M"-shaped deflections. Mispireta and associates,[14] found morphologic changes of the H and J waves, with increased depth of the K wave, and in the height of the entire I, J, L complex. These investigators noted an alteration in duration of the systolic waves. Bixby[15] reported the absence of the K wave in a single case of patent ductus arteriosus with return to normal following surgery.

In aortic stenosis both van Lingen and associates[16] and Dock and co-workers[8] call attention to an outward bowing or angulation of the J-K segment which was not masked even with superimposed aortic insufficiency.

Dock and associates[8] state that in pure pulmonic stenosis the amplitude of the ballistocardiogram is generally diminished, a finding which is contrary to that reported by others.[7,13] Frankel's group noted very deep H-I and I-J slopes, the latter exceeding the former by approximately 50 per cent regardless of the respiratory phase and with well-developed after-waves.[17] Rager and co-workers found a small amplitude of the H-I waves with an increase in the K wave during expiration.[13]

From the Cardiographic Laboratory and Department of Medicine, The Mount Sinai Hospital, New York, N. Y.

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*Fellow John Simon Guggenheim Foundation.

In cases with the tetralogy of Fallot, Rager and associates[13] found an increase of the amplitude of the H wave, regardless of the respiratory phase, associated with an increased depth of the I-J complex and a prolonged J-K segment.

Stimulation for this study was in part derived from the limited and divergent findings reported in the literature and was undertaken to determine the value of the ballistocardiogram in the diagnosis of congenital cardiac disorders.

MATERIAL AND METHODS

The study reported on includes a total of ninety cases of congenital heart disease (Table I). The ballistocardiogram was recorded with the dual ballistocardiograph.[18] Both photoelectric (displacement) and electromagnetic (velocity) records were obtained in every patient during slight inspiration, deep inspiration, and deep expiration. The analysis for this study was based only on the displacement ballistocardiographic tracings.

The diagnosis was established clinically and was confirmed by additional studies such as cardiac catheterization, angiocardiography, surgical exploration, etc. (see Table I). Only those cases where confirmatory evidence was strong were included in this study.

The ballistocardiographic criteria utilized have been detailed elsewhere.[19] The appearances of amplitude, slurring, notching, etc. were the sole factors which determined the normality or abnormality of the record.

TABLE I

DIAGNOSIS	NO. CASES	AGE (YEARS)	MALE	FEMALE	ADDITIONAL CONFIRMATION			
					CARDIAC CATHETERIZATION	ANGIOCARDIOGRAM	SURGERY	POST MORTEM
Coarctation of aorta	18	5–48	13	5	1	10	8	2*
Patent ductus arteriosus	10	3–42	6	4	2	—	10	1*
Interventricular septal defect	8	3–10	4	4	8	—	—	—
Aortic and subaortic stenosis	3	3–7	3	—	—	—	—	—
Interatrial septal defect	10	4–36	4	6	10	4	—	—
Pulmonic stenosis	10	6–44	5	5	10	5	3	—
Pulmonic stenosis with interatrial septal defect	5	6–32	4	1	5	3	3	—
Tetralogy of Fallot	12	8–32	5	7	12	7	7	2*
Eisenmenger complex	5	10–21	4	1	5	4	—	—
Tricuspid atresia	5	5–12	4	1	3	5	2	—
Congenital aneurysm of sinus of Valsalva	1	40	—	1	1	1	—	—
Aortic septal defect	1	19	—	1	1	—	—	—
Idiopathic dilatation of pulmonary artery	2	14–16	2	—	2	1	—	—
Total	90		54	36	60	40	33	5

*One case postoperatively.

RESULTS

I. *Coarctation of the Aorta.*—The ballistocardiograms in all eighteen patients were abnormal. The findings consisted of a small to absent K wave in eighteen and a deep I wave in fifteen (the depth of the I wave was inversely proportional to the depth of the K wave) (Fig. 1). In those cases which had surgical correction of the coarctation, the ballistocardiogram converted to normal. Details in this group will be reported in a later communication.[20]

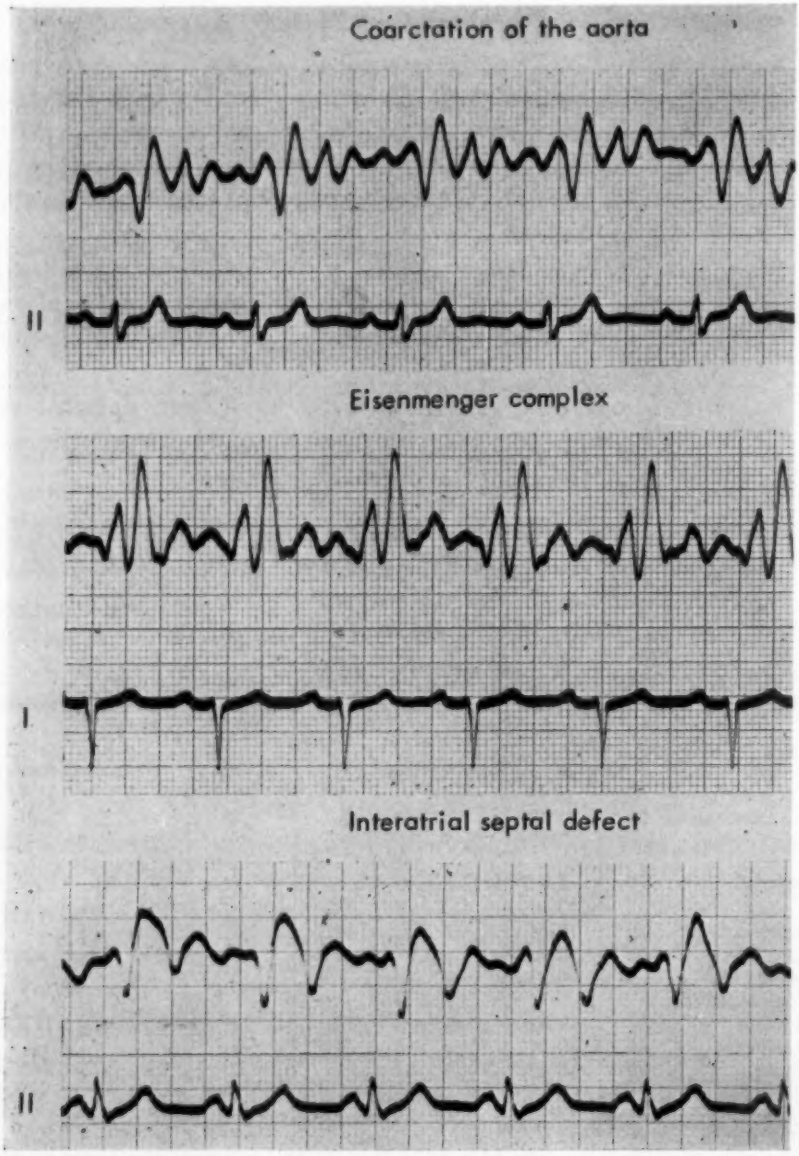

Fig. 1.—Ballistocardiograms of (*A*) L. R. (50-2443), (*B*) G. D. (7119), and (*C*) A. S. (36041) showing short K waves.

II. *Patent Ductus Arteriosus.*—Ten patients were studied and in only five was the ballistocardiogram abnormal. The abnormalities seen were as follows: two patients presented a small I wave with high or normal voltage, in one a short K wave was present, in another a small H wave and high voltage. In the remaining patient the record was bizarre.

III. *Interventricular Septal Defect.*—This group consisted of eight patients. The records were normal in five and abnormal in three. The abnormalities were different in each and consisted of an occasional short K wave in one, a small I wave in one, and a bizarre tracing in the other.

IV. *Congenital Aortic and Subaortic Stenosis.*—Though there were only three patients in this group, the record was normal in two. Notching of the upstroke in the J wave was observed in the third.

Pulmonic Stenosis

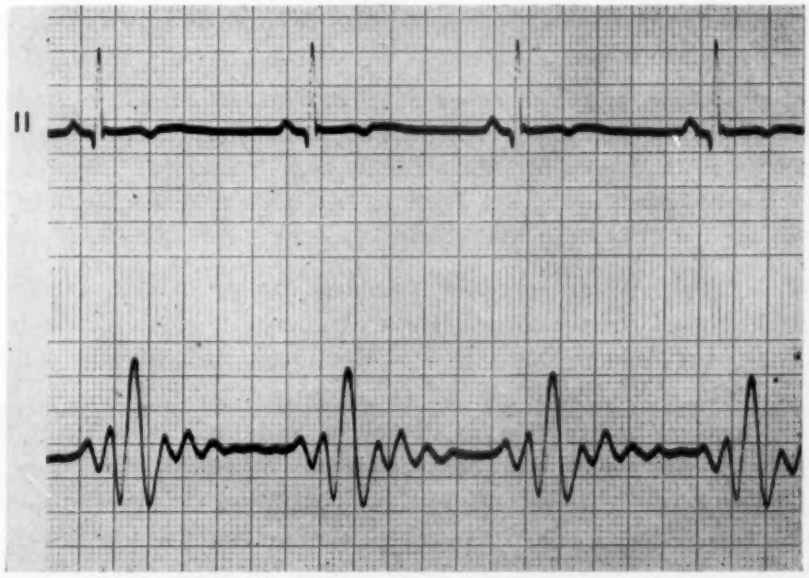

Fig. 2.—Normal preoperative ballistocardiogram in a patient with pulmonic stenosis (V.R. 27730).

V. *Interatrial Septal Defect.*—There were ten patients in this group and the records were abnormal in only six. The abnormalities consisted of a short K wave with normal or high voltage in three, a small I wave with normal or high voltage in two, and a bizarre record in one.

VI. *Pulmonic Stenosis.*—

A. *Isolated pulmonic stenosis:* The ballistocardiogram was abnormal in five of ten patients. The findings consisted of a very small I wave in three, an early "M"-shaped complex in one, and a slurring of the I wave with normal voltage in the other.

B. *Associated with interatrial septal defect:* The record was abnormal in three of five patients and varied from a very small I wave and low voltage in one, an early "M"-shaped complex in one, and a bizarre record in the other. It should be pointed out that of the fifteen patients in this group the voltage of the ballistocardiogram was normal or high in all but one (Fig. 2).

VII. *Tetralogy of Fallot.*—There were twelve patients in this group and only six presented abnormal records. The findings were as follows: a small I wave in two cases, a wide K wave in one, an absent I wave, tall L wave, and high voltage in one, a notched K wave in one, and a notched K wave with a small I wave in the other.

VIII. *Eisenmenger Complex.*—This group consisted of five patients and all had abnormal ballistocardiograms. The findings were as follows: a short K wave in two, short K wave with a small I wave in one, short notched K wave and prominent H wave in one, and a late "M" complex in the other (Fig. 1).

IX. *Tricuspid Atresia.*—The five patients studied in this group all presented abnormal records which consisted of a prominent H wave in four and a very small I wave in one.

X. *Miscellaneous.*—The other four patients with aortic septal defect, aneurysm of the sinus of Valsalva, and idiopathic dilatation of the pulmonary artery (two cases) had normal ballistocardiograms.

COMMENTS

In the various congenital cardiac anomalies studied as related to the ballistocardiographic curves, there were only three diagnoses in which relatively constant abnormalities were found; coarctation of the aorta, Eisenmenger complex, and tricuspid atresia.

Our findings in coarctation of the aorta and their conversion to normal following surgery are similar to those reported by others.[3-7]

The changes in the K wave have been attributed to a diminution of blood flow in the descending aorta.[21] However, similar changes have been reported in elderly patients with congestive heart failure, in aortic insufficiency, and in patients with hypotension and shock.[8] Other investigators have found essentially the same pattern in patients with intraluminal aortic obstruction.[9-12] Though Starr and his colleagues believed that the K wave seen in the high frequency ballistocardiogram represented an artefact,[22] it was the more recent work of Deuchar and associates utilizing an aperiodic bed to suggest that the K wave was secondary to after oscillation.[23] These investigators were unable to define K waves in normal individuals with their technique, though the same was present in the high frequency ballistocardiographic records.

The patients with the Eisenmenger complex also presented short K waves in four or five cases. We cannot offer an explanation for these similarities to the ballistocardiogram of coarctation of the aorta. The presence of a prominent H wave in four of the five patients with tricuspid atresia could possibly be related to hemodynamic alterations. Since the majority of the patients with tricuspid

atresia resemble, functionally, tetralogy of Fallot[24] one would expect similar changes for both. However, in our cases with tetralogy of Fallot the H wave was not prominent. It is interesting that, in the only case of tricuspid atresia without a prominent H wave, pulmonary stenosis was not present at the time of surgical exploration. Prominent H waves have also been reported in cases of myocardial damage of various etiologies.[1,23,26]

Though in the other congenital malformations the changes were inconsistent, there are two conditions that deserve consideration. First, in our patients with pulmonic stenosis, regardless of the normality of the ballistocardiogram, all patients except one presented normal or high-voltage complexes. These findings differ with the statement made by Dock.[8] Secondly, in the subjects with aortic stenosis, only one of our three patients presented any abnormality. Admittedly such a series is small; it does however illustrate the point that a normal ballistocardiogram does not in itself exclude a diagnosis of aortic stenosis as has been reported.[8,16]

SUMMARY

1. The ballistocardiogram in varied congenital cardiac malformations has been presented and discussed.

2. Short K waves are uniformly present in coarctation of the aorta, but this finding is not specific since patients with interatrial septal defect, Eisenmenger complex, and patent ductus arteriosus may display similar findings.

3. Pulmonic stenosis does not produce low amplitude abnormal ballistocardiographic patterns, as has been reported. The record often is entirely normal and actually may be characterized by increased voltage.

4. Tricuspid atresia produces prominent H waves.

5. The other congenital cardiac malformations studied do not produce specific abnormalities.

6. In our opinion the ballistocardiogram has little practical value in the study of congenital cardiac malformations.

SUMMARIO IN INTERLINGUA

1. Es presentate e discutite le ballistocardiogramma in varie congenite malformationes cardiac.

2. Breve undas K es uniformemente presente in coarctation del aorta, sed iste constatation non es specific, proque patientes con defecto del septo interatrial, complexo de Eisenmenger, e patente ducto arteriose pote exhibir tractos simile.

3. Stenosis pulmonar non produce, como ha essite reportate, anormal configurationes ballistocardiographic a basse amplitude. Frequentemente le registration es completemente normal, e illo pote mesmo esser characterisate per voltage augmentate.

4. Atresia tricuspide produce prominente undas H.

5. Le altere congenite malformationes cardiac que nos ha studiate non produce anormalitates specific.

6. Secundo nostre opinion le ballistocardiogramma ha pauc valor practic in le studio de congenite malformationes cardiac.

We appreciate the angiocardiograms performed by Dr. Sigmud Brahms, and the release of the cardiac catheterization data for this study by Dr. Alvin J. Gordon. Also thanks to Miss Iris Kanner for her technical assistance.

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LEFT HEART CATHETERIZATION

I. Clinical Methods and Applications

James Bougas, M.D., Benjamin G. Musser, M.D.,* and
Harry Goldberg, M.D.

Philadelphia, Pa.

RAPID progress in cardiac surgery has created the need for more precise preoperative evaluation of intracardiac hemodynamics. Although right heart catheterization gives some information in mitral valvular disease, it is of little or no value in assessing the dynamics at the aortic valve. Left heart catheterization offers physiologic data in mitral and aortic valvular disease not previously available. Its techniques are being modified and developed. Its results are being analyzed. The value of this procedure in clinical diagnosis and assessment of the pathologic physiology of valvular heart disease is being formulated.

Facquet and associates[1] and Allison and Linden[2] measured left atrial pressures by transbronchial routes. Björk[3,4] described the transthoracic technique for direct left atrial puncture and catheterization. The use of the prone position and fluoroscopy during insertion of the needle was suggested by Kent and associates.[5] Left atrial puncture was also accomplished through the suprasternal notch.[6]

Experiences with 127 consecutive left heart catheterizations in 120 patients constitute the subject of this paper. Since the indications and contraindications of this procedure are undetermined at present, patients considered to have clinically significant lesions of the mitral and aortic valves were selected for this study. There were two patients who were considered to have normal cardiovascular systems included. Subsequently, 90 per cent of the patients catheterized had cardiac surgery, thereby providing operative correlation for the physiologic data.

PREMEDICATION

Patients selected for catheterization were maintained in a fasting state for four to twelve hours. To reduce apprehension, ameliorate discomfort, and establish more "basal" conditions, premedication was utilized. Demerol, 50

From the Brith Sholom Cardiopulmonary Laboratory and the Departments of Medicine and Thoracic Surgery, Hahnemann Medical College and Hospital, Bailey Thoracic Clinic, Philadelphia, Pa.

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mg. intramuscularly, and Seconal, 90 to 180 mg. by mouth, were given one to two hours before the study. Choice of these drugs was empirical.

POSITION AND APPROACH

The first four of our patients who had direct left heart catheterizations were investigated in the left lateral decubitus position described by Björk.[3,4] The approach was made through the right eighth intercostal space to the right of the spine. However, it was soon apparent that variations in body habitus and cardiac contour made necessary a more accurate method. Early difficulties in left atrial puncture occurred, particularly in patients with aortic valvular disease in whom the left atrium was not enlarged. All patients, after the first four, were catheterized in the prone position as described by Kent and associates.[5]

ATRIAL PUNCTURE AND CATHETERIZATION

Catheterization was performed through a sharp 18-gauge thin-walled Styletted needle 6 inches long.* A suitable intercostal space, usually the eighth or ninth, was selected fluoroscopically. The site of the needle puncture, 4 cm. to the right of the dorsal spinous process, was infiltrated with 1 per cent procaine to the depth of the intercostal space. The atrial puncture needle was passed to a point just beyond the transverse process of the vertebra and fluoroscopic check made. The angle for entry of the left atrium was approximately 20 degrees from the vertical in the coronal plane. With a large left atrium, insertion of the needle could be made in a more vertical direction. The styletted needle was advanced slowly until a definite snap was felt at the point of entry through the pericardium and atrial wall. Marked indentation of the atrial wall occurred in many of those patients with a normal left atrium and was appreciated as a sense of gradually increasing resistance to the advancing needle. Atrial premature systoles were frequently observed as the needle invaginated the left atrium.

Calcification of the atrial wall was recognized in one of our patients and puncture was noticeably more difficult. In several others, the wall was thickened and lined by organized thrombi. Needle puncture did not precipitate subsequent emboli in any case. The presence of atrial thrombus was detected at surgery in six patients in this series; its presence was predicted at the time of catheterization in three cases. In these, definite snapping sensation was appreciated upon entry into the atrium. However, a free flow of blood was obtained only after advancing the needle an additional centimeter or two. Aspiration through the needle produced small fragments of organized thrombus.

Polyethylene, polyvinyl, or Nylon catheters, designed to pass through the needle readily, are available. The polyethylene catheters are more flexible and are particularly useful in entering the aorta. On the other hand, we have not succeeded in passing the polyvinyl or Nylon catheter into the central aorta. These catheters are more rigid, and advance into the left ventricle has produced frequent premature ventricular beats and short runs of ventricular tachycardia.

*Thin-walled needles and catheters are available through Becton, Dickinson and Company, Rutherford, N. J.

They have been most useful in the study of mitral regurgitation. The rigidity allows more accurate direction through the mitral orifice.

In those patients with pure mitral disease, catheterization of the aorta was not attempted routinely. In those suspected of having aortic valvular disease, attempts were made to pass the catheter through the ventricle into the aorta. A measurement of the gradient across the aortic valve was obtained in this way.

Intracardiac and intravascular pressures were recorded with electromanometers and a polyoscillograph (Sanborn). Oscilloscopic monitoring of the electrocardiogram and of the pressures during manipulation of the catheter was considered mandatory. Recently, simultaneous pressures were recorded in the left atrium and ventricle by inserting a second needle parallel to the first. This is particularly useful in patients with atrial fibrillation.

The polyethylene catheter is passed through the needle into the aorta. The needle may then be removed. With the catheter left in place the patient can be made to exercise. After the patient ceases exercising the catheter may be immediately withdrawn with continuous pressure recordings being made from aorta to left atrium. This has been done on many occasions without any undue effects.

A thoracic surgeon was either a member of the catheterization team or immediately available for any eventualities.

DISCUSSION

The first seven patients catheterized had predominant mitral regurgitation. They were selected as subjects because the large left atrium formed a sizable target for needle puncture. It became clear later that although entry into the left atrium was a simple problem in this group of patients, the passage of a catheter into the left ventricle frequently required from thirty to sixty minutes of manipulation. It was found that the stiffer polyvinyl or Nylon catheter usually succeeded when the polyethylene catheter failed to pass through the mitral orifice. Not uncommonly, the catheter passed into the ventricle only to be whipped back into the atrium several times, presumably by a jet of blood during ventricular systole. In four patients having giant atria, the catheter failed to enter the ventricle.

Emphasis was then turned to patients with aortic stenosis but with concomitant mitral stenosis, giving again a large left atrium for a target. As confidence in performance of the procedure was gained, patients with aortic stenosis and normal-sized left atria were catheterized (Fig. 1). Previously, with a large atrium, puncture had been directed at the estimated juncture of its middle and lower thirds in order to avoid the base of the aorta. This low aim at a small left atrium resulted in puncture of the right atrium or inferior vena cava (Fig. 2). By redirection of the needle in a more cephalad direction, left atrial puncture was accomplished.

With this experience in mind, several deliberate attempts were made to enter the atrium in its upper portion. In this position, subsequent passage of the catheter was difficult. The catheter jammed against the opposite atrial wall as it was advanced to the level of the needle tip. Since no untoward effects

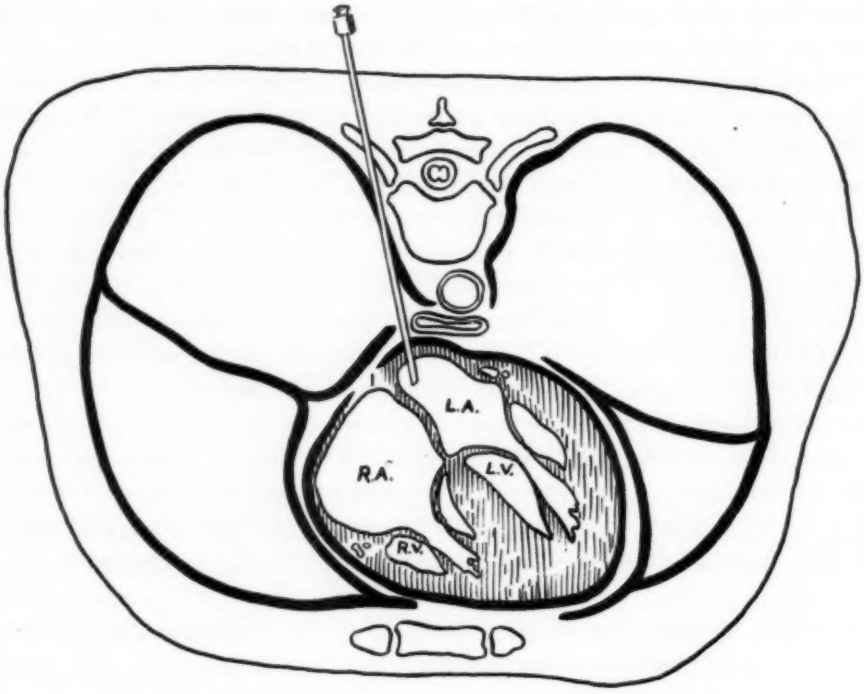

Fig. 1.—Percutaneous approach in a normal left atrium.

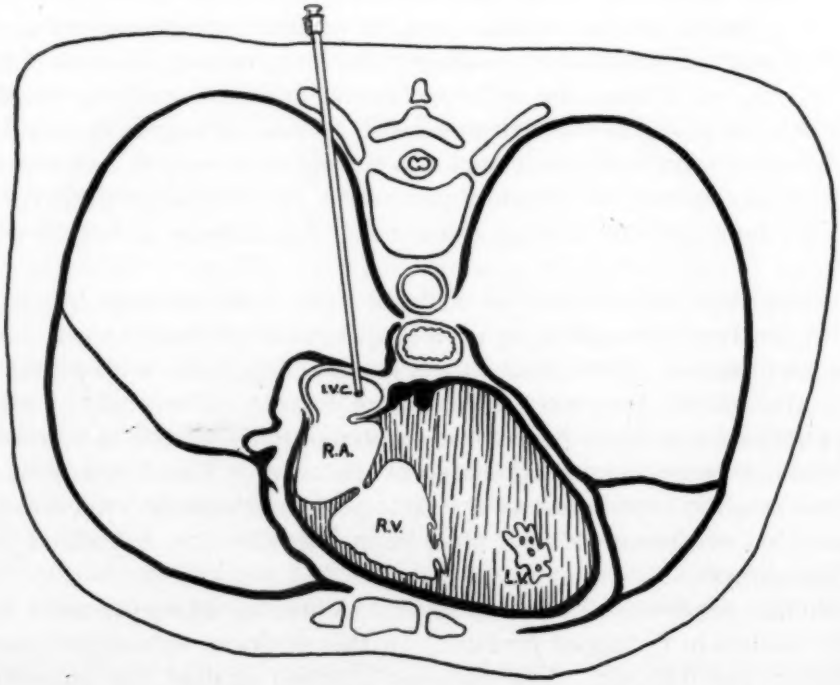

Fig. 2.—Entry of right heart via inferior vena cava with low approach.

had followed the inadvertent entries into the right atrium, the point of aim was lowered to the approximate center of the left atrium. When a left atrial contour was not evident on fluoroscopy, the right bronchus and the right pulmonary artery, together with the general cardiac contour, were used as guides. Usually, the intercostal space of choice was two and one-half intercostal spaces cephalad to the right diaphragm in midrespiration and one intercostal space caudad to the right pulmonary artery.

Invagination of the atrial wall by pressure of the advancing needle was observed frequently (Fig. 3). Rotation of the needle on the atrial wall was used to penetrate the pericardium and myocardium so as to diminish the amount of invagination. Not uncommonly, the invaginated atrial wall rebounded around the penetrating needle leaving the point near the opposite wall or septum. It was then necessary to withdraw the needle a centimeter or two to permit unobstructed passage of the catheter into the atrial chamber.

Fig. 3.—Invagination of left atrial wall and pericardium before the advancing needle. This may result in entry of right atrium.

Entry into the right atrium was made several times through the interatrial septum when the wall was sharply invaginated (Fig. 4). No difficulty ensued. Slow withdrawal of the needle, while intermittent aspiration was performed with a syringe, brought the needle point again into the left atrium to allow left heart catheterization. An unintended direct entry occurred into the bulging right atrium of a patient with both mitral and tricuspid stenosis. It was possible in this case to catheterize both right and left sides of the heart. The transseptal right atrial punctures and the one right atrial entry by caudad direction of the needle tip prompted interest in the planned simultaneous right and left heart catheterization through the back when roentgenology demonstrated an enlarged right atrium. A caudad and more vertical redirection of the left atrial

needle or the use of a second needle, so directed, makes possible, in selected cases, a bilateral heart catheterization complete with blood samples for gas analysis. Conventional venous approach is definitely preferred in catheterizing the right heart.

In studies during the early part of this series, the polyvinyl catheters would tend to catch on the needle, while the catheter was being withdrawn. This difficulty was obviated at the time by simultaneous withdrawal of the catheter and needle, thereby avoiding the possibility of intracardiac amputation of the catheter. However, rounding of the edge on the inner wall of the needle tip adequately solved this problem. Now, free passage of the catheters through the needle is secure as long as gentle handling is used to prevent kinking.

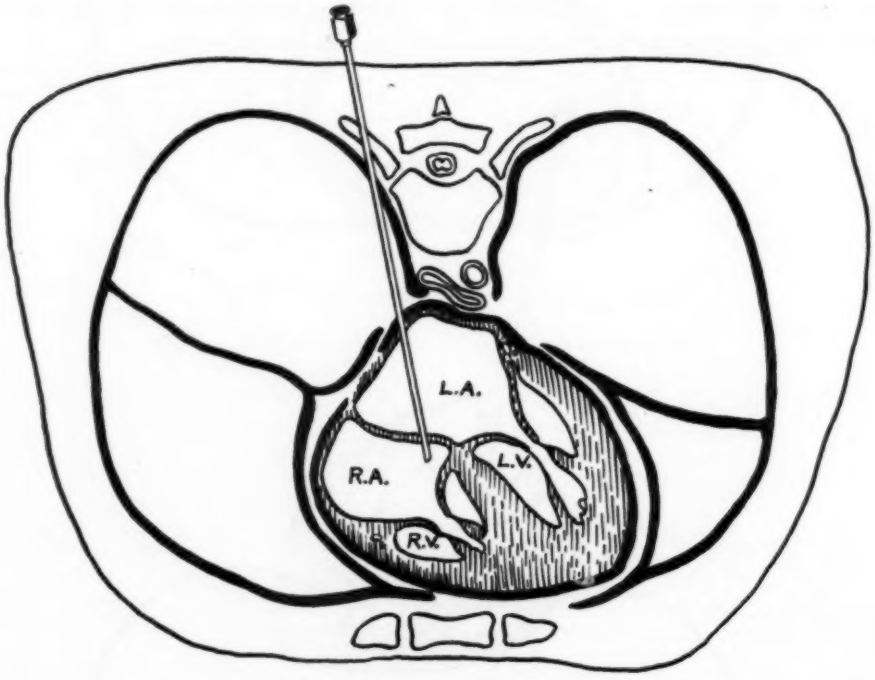

Fig. 4.—Transseptal approach to right atrium. In an enlarged left atrium, the interatrial septum lies more perpendicular to the needle.

Two patients having Lutembacher's syndrome were catheterized by the left atrial route as well as by the conventional right heart route. In both cases, it proved impossible to direct the catheter through the mitral orifice, although complete right heart catheterization was obtained by the catheter, which passed through the septal defect with facility.

Five unintentional direct punctures were made into the base of the aorta distal to the valve (Fig. 5). The first two occurred while catheterization was being performed in the lateral position without fluoroscopic guidance. The third was in a patient with huge aneurysmal dilatation of the ascending aorta. The fourth and fifth occurred during a high approach to a small left atrium.

In all cases, the patients suffered sharp discomfort referred substernally. Hypotension of several hours' duration was noted in the first two. Recovery was complete in both, although one required noradrenalin intravenously intermittently for eight hours. The third patient had no change in vital signs and was ambulatory, but received codeine during the ensuing thirty-six hours. The fourth patient had discomfort of milder degree, but developed a sinus tachycardia which persisted for one hour. The fifth patient became asymptomatic in twenty-four hours. The use of fluoroscopic guidance of the needle has reduced the incidence of aortic puncture. The descending aorta was avoided in one patient who had a right-sided aorta, by inserting the needle through the left hemithorax. The presence of aneurysmal dilatation of the aorta can be considered a contraindication for direct left atrial puncture.

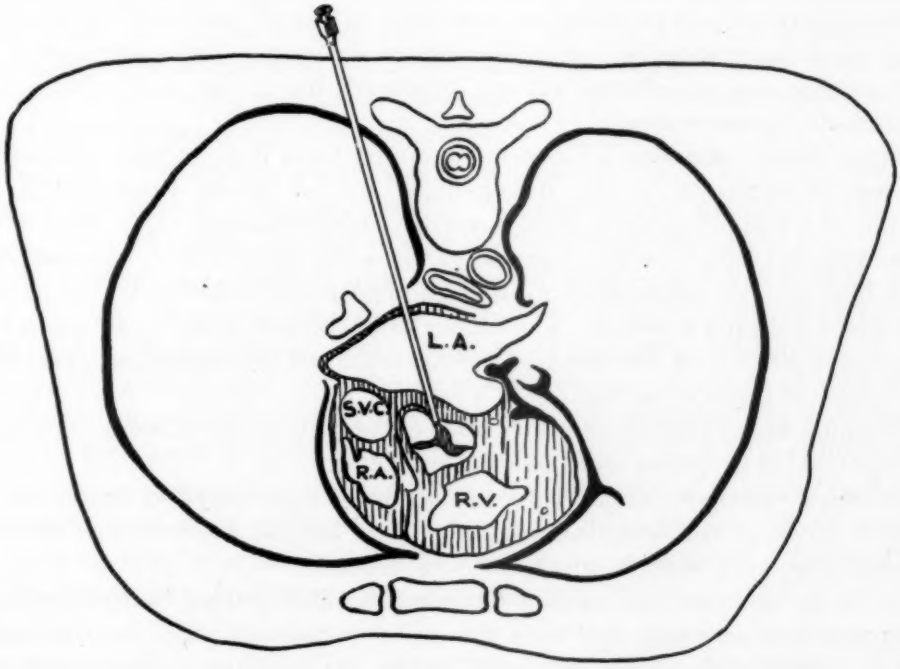

Fig. 5.—Transatrial entry into ascending aorta during high approach.

Sensations transmitted through the needle can be of great help. A definite systolic vibration is felt from the aortic wall. A much softer systolic thrill is felt from the left atrial wall in patients with severe mitral valve regurgitation. Usually, in mitral stenosis or milder mitral insufficiency, the hypertrophied atrial wall gives an impression of a heaving rubbery tissue which, at the same time, gives ground to the advancing needle tip.

Following the procedure, patients are returned to their rooms and are instructed to remain recumbent for two hours. Earlier, oral intake was restricted for two hours, but more recently this regimen has been discontinued without evident ill effect.

COMPLICATIONS

On contact of the needle tip with the pericardium and atrial wall, the patient frequently had a sensation of pressure in the upper substernal region. A "sticking" sensation has also been noted in the suprasternal notch. These symptoms are suddenly relieved or ameliorated as the needle snaps into the atrium. This discomfort is usually so minor as to be adduced only on questioning of the patient. The sensation of mild substernal pressure has persisted for as long as three days in one patient.

Staining of the pericardial fluid with relatively small amounts of blood occurred in 80 per cent of the cases subsequently explored. Such limited hemopericardium did not produce late symptoms or any change in vital signs. Probably, it failed to appear in some cases because the needle puncture was near a pulmonary vein where there was no free pericardial space.

Hemopericardium produced hypotension in one of the aortic entries. The hypotension was treated with noradrenalin intravenously for eight hours. Pericardiocentesis was considered, but not employed due to the patient's continued symptomatic improvement.

Hemothorax occurred six times. Four patients had a single thoracentesis each with removal of 75, 75, 100, and 300 c.c. of blood, respectively. Two patients had a right pleural effusion before catheterization. The first of these required daily aspirations for eleven days following the left heart catheterization; at first bloody, later serous fluid. The second patient required four thoracenteses, all of which contained blood. The hemoglobin content of the fluid was 4.5 Gm. A total of 1,800 c.c. of this fluid was aspirated from the right chest; transfusion was needed to replace the loss.

Pneumothorax was observed in three cases. All of these were minimal and required no therapy other than codeine analgesia.

Hemoptysis occurred in three patients. These resulted probably from needle wounds of the bronchus or lung. The longest duration of hemoptysis was two days. No specific treatment was needed.

In a recent case, the catheter became wedged during withdrawal. The needle was first removed, and then the catheter was dislodged by traction. It was then noted that a knot had been tied in the catheter. There were no sequelae, and thoracotomy was not necessary. Björk has reported a similar complication while using two catheters, and thoracotomy was required for removal.[3] In view of these experiences, whenever two needles were used, one catheter was advanced only to the tip of the needle, while the other was advanced to the left ventricle or aorta.

Syncope has accompanied rapid changes in position on two occasions after completion of the catheterization. The patients are instructed to remain recumbent for two hours following the procedure.

Pyrogenic reaction to catheterization has been observed in one patient with a fever of seventy-two hours' duration. Although earlier patients received no antibiotics and no difficulties ensued, on empirical grounds, a suitable antibiotic is now recommended and is given prophylactically for forty-eight hours following catheterization.

Diminished ventilation was produced in some patients by the combination of the premedication and the prone position. In several of these patients, decreased oxygen saturation was observed in the peripheral arterial blood. At no time, however, was it necessary to conclude the study because of ventilatory difficulty.

A patient with mitral regurgitation, the third of those catheterized in the lateral position, expired twelve hours after the study. An episode of hypotension and brief syncope occurred after conclusion of the catheterization. Arrhythmias were not observed on the electrocardiogram at that time, nor clinically at any time prior to death. The hypotension was transient and disappeared without specific therapy after several minutes. The patient then remained clinically well until the time of her sudden death. Autopsy examination revealed the site of atrial puncture to be well placed and sealed, with no evidence of hemorrhage into the pleural or pericardial spaces. The heart was markedly enlarged with a dilated mitral annulus resulting in severe mitral regurgitation. This is the only death in our series, and the third which has been reported, subsequent to left heart catheterization, in the literature.[3,6]

Pressures in the left atrium have been studied during rest, exercise, and change in position. Pulmonary capillary pressures and contours have been compared with simultaneously recorded left atrial measurements.[8]

Left heart catheterization, when combined with estimation of the cardiac output by right heart catheterization (direct Fick), can provide data hitherto unobtainable.[8] Simultaneous measurements of pressure gradients and flow across the stenotic orifices allow for estimation of ventricular work and orifice size. This is of particular value in assessing the dynamics of aortic valvular disease in which right heart catheterization alone gives little or no information.

Simultaneous catheterization of the left and right heart has been performed in a series of patients with mitral and aortic valvular disease. Some of these patients have been studied before and after valvular surgery. These studies will form the subjects of subsequent communications.[8]

SUMMARY

1. The technique, premedication, and approach for left heart catheterization have been presented. Problems pertaining to left atrial puncture have been described, and suggestions made.

2. Our experiences in 127 such consecutive procedures in 120 patients have been outlined.

3. The complications have consisted of hemopericardium (80 per cent) of no clinical significance, requiring no specific therapy. Hemothorax occurred on six occasions, pneumothorax in three. Sudden death occured in one patient twelve hours subsequent to the procedure.

ADDENDUM

Two hundred and ninety additional left heart catheterizations were performed subsequently and will be included in a future report.

SUMMARIO IN INTERLINGUA

1. Es presentate un description de technica, premedication, e via de accesso in catheterisation sinistro-cardiac. Es describite problemas relative a punction sinistro-atrial. Suggestiones pertinente es facite.

2. Nos delinea nostre experientias in 127 consecutive interventiones de ille genere, interprendite in 120 patientes.

3. Le complicationes consisteva de hemopericardio (80 pro cento) sin signification clinic e requirente nulle therapia specific. Hemothorace occurreva a sex occasiones, pneumothorace a tres. Morte subitanee occurreva in un patiente dece-duo horas post le intervention.

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A CLINICAL STUDY OF COMPLETE HEART BLOCK

JAMES C. WRIGHT, M.D., M. R. HEJTMANCIK, M.D., GEORGE R. HERRMANN, M.D., AND ALLEN H. SHIELDS, M.D.

GALVESTON, TEX.

COMPLETE atrioventricular heart block is a very serious cardiac mechanism disorder and is generally considered to be a reliable sign of heart disease. It may occasionally be present for years without producing any symptoms or signs other than the regular slow heart rate and pulse. Slight giddiness and vertigo gradually develop but syncope and convulsions are fortunately less common complications, so that complete heart block and Adams-Stokes disease are not synonymous. The etiologic and pathophysiologic factors vary in both and may be changing with the decades. Electrocardiographic studies, which have become more frequent and more extensive, are required for certain diagnoses and have revealed interesting information. Newer and more effective drugs have been introduced and the prognosis has been slightly improved.

The restudy of the subject, therefore, is in order from time to time in every cardiovascular service, in the hope that the known facts will be substantiated, important clinical points emphasized, and the most effective, yet safe, therapeutic procedures established. To this end, we undertook the detailed analysis of the records of ninety patients with complete heart block studied in the University of Texas Hospitals during the past twenty-five years.

The prerequisite for inclusion in this study was electrocardiographic proof of complete heart block (Fig. 1,*B*), consisting of the presence of two independent pacemakers, with the supraventricular focus of faster rate than the idioventricular focus to rule out functional A-V block, as in interference dissociation.

Of 150 records originally diagnosed as complete heart block, only ninety cases fulfilled the criteria outlined. Thus complete atrioventricular heart block, meeting our criteria, was a relatively rare cardiac mechanism disorder, occurring only ninety times in 49,000 patients on whom electrocardiographic studies were made.

ETIOLOGICAL DATA

The age and sex distributions in our cases, shown in Fig. 2, are in general agreement with the data of three comparable series.[3,5,9] These data show that the condition occurs more often in the older age groups, and more often in men.

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Our ratio of men to women was about 1.5:1, which is somewhat lower than generally reported.

Etiologically our cases were divided into two large categories (Table I): The first group in which digitalis intoxication was the major factor; the second group in which digitalis had not been used. This second group was then subdivided into: established complete heart block, of four weeks' duration or longer by ECG as well as clinical observation; transient complete heart block; and complete heart block of undetermined duration, the latter to include those cases where the observation period was too short or information insufficient to accurately establish the duration of the conduction defect.

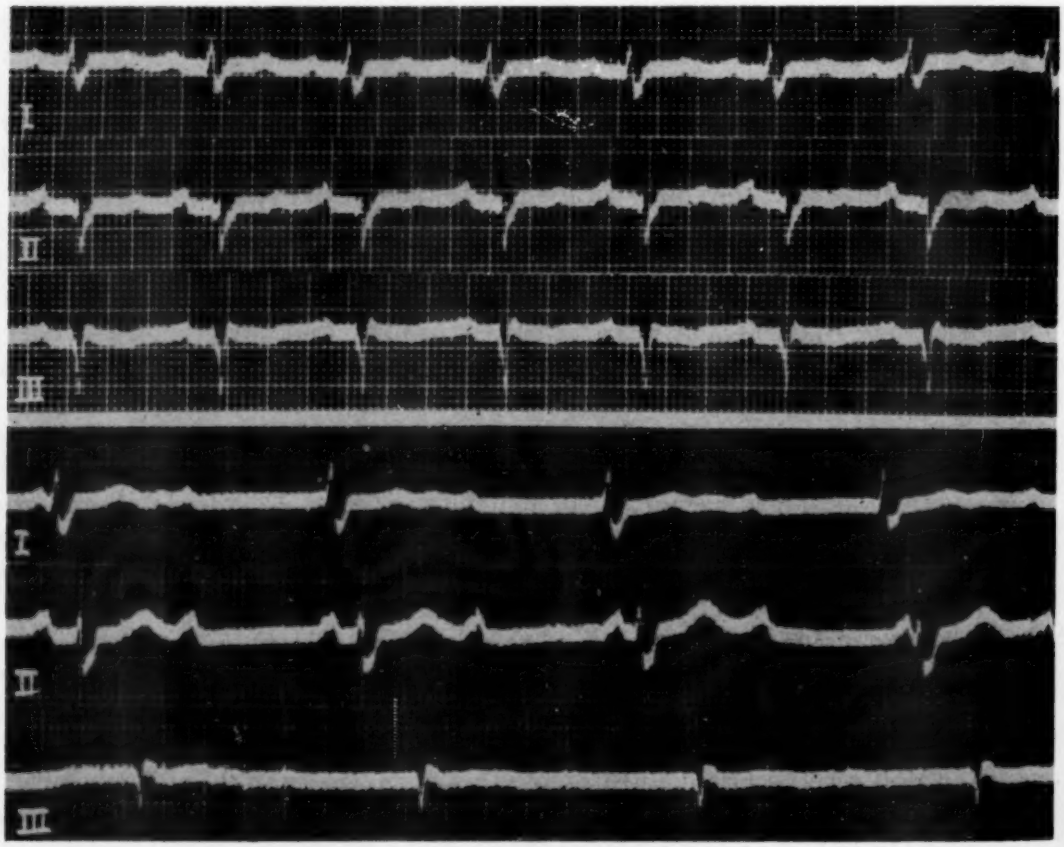

Fig. 1.—A 64-year-old white woman. *A*, Tracing taken (1945) one year before the onset of complete heart block showing supraventricular rhythm (prolonged A-V conduction) and right bundle branch block. *B*, (1946) Complete heart block, with similar QRS configuration. Atrial rate 84 per minute; ventricular rate, 43 per minute.

Of the various etiological factors, summarized in Table I, atheromatous coronary artery disease, alone or in combination with hypertensive arteriolar disease was, by far, the most common cause. The less frequent etiologies included syphilitic valvulitis in eight patients and rheumatic valvulitis in seven patients. In the group of patients showing "established" complete heart block, diphtheria was the probable etiology in two cases, and a congenital origin was

diagnosed in three patients. In this same group two patients were classed under the "unknown" etiology. Of these, one was thought to have had previously either a diphtheritic or rheumatic process, and the other, in all likelihood, was congenital.

Acute myocardial infarction was present in nine patients, six, or two-thirds, of whom died within forty-eight hours after the appearance of complete heart block, confirming the general impression that development of this conduction defect in acute myocardial infarction indicates a poor prognosis. Terminal uremia was a major added factor in eight patients in whom the heart block generally developed shortly before death.

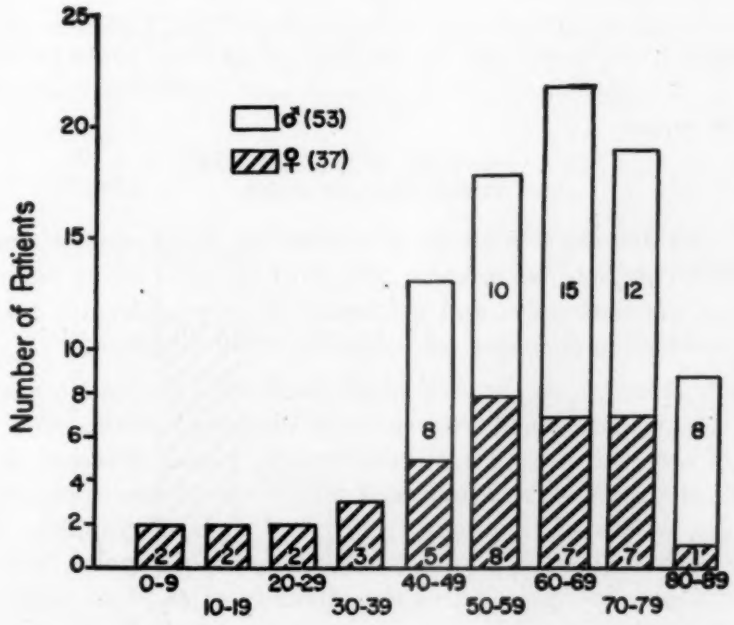

Fig. 2.—Age and sex distribution of ninety patients with complete heart block.

There have been several other reported causes of complete heart block including hyperthyroidism,[15] various infections other than diphtheria,[4,18] and gummatous[7] or neoplastic invasion of the heart.[1] It has also been reported in cases of Paget's disease, due to calcification of the interventricular septum.[6] One case of complete heart block in this series suffered from Paget's disease and presented evidences of advanced medial as well as atheromatous disease, but unfortunately autopsy was not permitted so that calcification of the septum could not be substantiated.

In the twenty-two cases with autopsy findings, the clinical etiological diagnoses were confirmed, but no detailed serial section studies of the cardiac conduction system were made.

TABLE I. COMPLETE HEART BLOCK

PROBABLE ETIOLOGY	DIGITALIS CASES	NONDIGITALIS CASES		
		ESTABLISHED	TRANSIENT	UNKNOWN DURATION
Arteriosclerosis	12	16	8	6
Arteriosclerosis and hypertension	7	10	1	2
Hypertension	—	—	—	1
Luetic H.D.	4	4	—	—
Rheumatic H.D.	4	3	—	—
Pulmonary H.D.	2	—	—	—
Diphtheria	—	2	—	—
Congenital	—	3	—	—
Unknown	2	2	1	—
Total Cases	31	40	10	9

H.D. = Heart disease.

SYMPTOMS AND SIGNS

Clinical and radiologic findings of underlying heart disease were common in patients with complete heart block, the most frequent being angina pectoris, cardiac failure, cardiomegaly, and evidences of arteriosclerotic aortic disease. The various underlying etiologies were usually easily diagnosed.

Symptoms referable to the A-V block itself were present in approximately 50 per cent of patients (excluding cases of digitalis intoxication). Of these, about half (25 per cent of the total) exhibited the classic syncopal or convulsive attacks, while the remainder experienced milder symptoms of occasional giddiness or vertigo, or easy fatiguability. Physical signs of complete heart block were usually present, including the slow, usually regular pulse, and high pulse pressure. Occasionally, variation of the intensity of the first heart sound was noted. Faint sounds of atrial beats, with corresponding "a" waves in the jugular pulse were also observed.

ANALYSIS AND DISCUSSION OF ELECTROCARDIOGRAPHIC FINDINGS

In this study, the electrocardiograms of all cases were analyzed. Where available, tracings taken before or after a transient episode of complete block, or those taken prior to the onset of established complete heart block, were also reviewed. Such analysis has brought out some points not especially emphasized in previous reports.

In the thirty-one cases of complete heart block due to digitalis intoxication, supraventricular mechanism disorders were quite common; atrial fibrillation occurring in sixteen, and atrial tachycardia in four of these patients. Such arrhythmias were quite uncommon in complete heart block of the other etiologies. In general, the rate of the idioventricular pacemaker was higher in heart block due to digitalis intoxication as compared to those cases due to other causes.

In patients with acute myocardial infarction, definite ECG evidences of such infarction were usually present, despite the presence of complete heart block and an idioventricular pacemaker.

Other evidences of ECG abnormality, including S-T-T wave changes, signs of ventricular hypertrophy, evidence of infarction and of 1 or 2 degree heart block were common in the preliminary or follow-up tracings of patients exhibiting complete heart block, as should be expected from the underlying causative heart disease.

Previous electrocardiograms taken within two years of the onset of complete heart block were available in forty-four patients in this series. In 43 per cent of these patients, bundle branch block antedated complete heart block (Table II).

Furthermore, it became evident that because of pre-existing bundle branch block, a broad, bizarre idioventricular complex in complete heart block did not, per se, indicate a pacemaker situated low in the specialized tissue, as has been inferred by many authors.

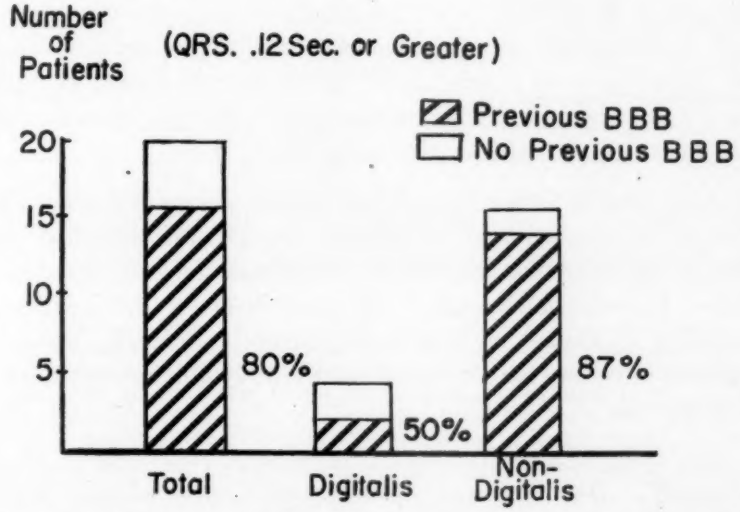

Fig. 3.—Wide idioventricular complexes in complete heart block. Bundle branch block present with supraventricular conductions before the development of complete A-V block, was felt responsible for the broad QRS complexes later found in the complete heart block tracings in sixteen of twenty cases.

There were twenty patients in our series who showed such wide bizarre QRS complexes in their heart block tracings (such a case is illustrated in Fig. 1). ECG's taken before the onset of complete heart block revealed pre-existing bundle branch block in 80 per cent of these patients (Fig. 3). There was a much higher percentage of bundle branch block in the cases of complete A-V block not associated with digitalis intoxication. The only two exceptions in this group occurred in patients with acute myocardial infarctions, in which the additional presence of a bundle branch block could not be excluded.

These data indicate that the QRS duration or configuration is an unreliable index of the relative position of the idioventricular pacemaker, and the presence of broad, slurred, or notched QRS complexes in complete heart block does not necessarily indicate a very low pacemaker, but rather, more commonly, the broad QRS represents a coexisting bundle branch block.

TABLE II. BUNDLE BRANCH BLOCK PRECEDING COMPLETE HEART BLOCK

	DIGITALIS	NONDIGITALIS	TOTAL
Total cases with previous ECG	22	22	44
Incomplete BBB preceding heart block	2 } 18%	3 } 68%	5 } 43%
Complete BBB preceding heart block	2 }	12 }	14 }

MANAGEMENT

The management of patients with complete heart block depends on the presence or absence of symptoms referable to the mechanism disorder itself. As long as the ventricular pacemaker is stable, at a rate of 30 or more beats per minute, no attacks are experienced and no specific therapy is necessary. It is a good policy, however, to try routinely to increase coronary blood flow by the use of vasodilators, and to avoid the use of any myocardial depressives or sedatives, including such bradycardic agents as bile salts. If digitalis intoxication is present, all digitalis should, of course, be promptly discontinued, at least temporarily, and full doses of atropine prescribed.

In the acute Adams-Stokes attack, the usual emergency measures should be employed, including sharp blows to the precordium, pricking the ventricle with a needle, or the intracardiac injection of various drugs.[8] Isuprel, (isopropyl norepinephrine) is perhaps the safest effective drug for intracardiac injection,[11] but is not readily available, so that epinephrine is generally used. If present, a Zoll stimulator may be tried.[19] If clinically advisable, direct cardiac massage should be attempted.

TABLE III. DRUG THERAPY IN ESTABLISHED COMPLETE HEART BLOCK

DRUG USED	SEVERE SYMPTOMS		MILD SYMPTOMS		TOTAL	
	NO. CASES USED	BEST RESULT	NO. CASES USED	BEST RESULT	NO. CASES USED	BEST RESULT
Isuprel	6	4	7	4	13	8
Isuprel and ephedrine	2	1	1	1	3	2
Isuprel and atropine	3	2	2	2	5	4
Isuprel, ephedrine, and atropine	3	0	1	1	4	1
Ephedrine	5	2	2	1	7	3
Ephedrine and atropine	2	1	–	–	2	1
Ephedrine with digitalis	1	1	–	–	1	1
Atropine	2	0	–	–	2	0
Digitalis	2	1	1	1	3	2
Adrenalin in oil	1	1	–	–	1	1
Miscellaneous	8	0	1	0	9	0
Total		13		10	50	23

After the patient has survived one syncopal attack, steps should be taken to prevent recurrences, in general by the use of various drugs, the choice of drug depending, in part, on the cardiac mechanism producing attacks. In Table III are summarized our experiences in the drug therapy of symptomatic complete heart block in twenty-three patients.

In the majority of patients who exhibit symptoms of complete heart block, sudden ventricular asystole is the responsible mechanism. In others, symptoms may result from gradual slowing of the heart rate to below a critical level.

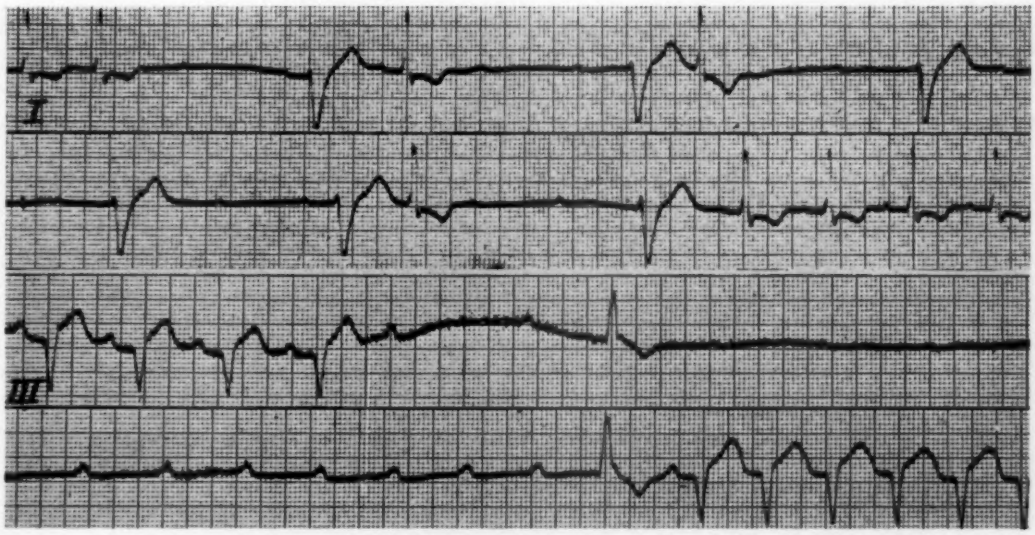

Fig. 4.—A 41-year-old woman who exhibited repeated Adams-Stokes attacks, resulting from periods of asystole or marked slowing of the heart rate occurring during a change from partial to complete heart block. Death finally resulted following progressive slowing of the ventricular pacemaker from 40 per minute to 20 per minute, to 10 per minute despite all therapeutic measures.

In these patients, the sympathomimetic amines, including epinephrine and its related compounds, are efficacious. Isuprel, in 10 or 15 mg. sublingual doses, alone or in combination with atropine and ephedrine, has been found in our studies to be most effective. Unfortunately, Isuprel frequently must be repeated as often as every hour or two. Monosodium lactate intravenously has recently been reported to increase the rate of the idioventricular pacemaker.[2] Atropine is generally given to offset whatever vagal effects may be inhibiting the idioventricular pacemaker.

Occasionally, symptoms may result from ventricular asystole occurring in a transition from partial to complete A-V block (Fig. 4). If the usual measures are unsuccessful, attacks may, at times, be prevented by digitalization during a period of complete A-V block, thereby fixing the block, and thus establishing a more stable pacemaker, often at a higher rate.

Parkinson, in 1941,[13] emphasized the frequency of ventricular acceleration as the mechanism producing Adams-Stokes attacks.[14] Such a mechanism of ventricular tachycardia, prefibrillary mechanism, or ventricular fibrillation was

felt to be responsible for severe attacks in three of our patients (Fig. 5). A mechanism of ventricular fibrillation may be suspected clinically when a prefibrillary acceleration is noted by the patient or by the physician, in contrast to those attacks which occur with an abrupt change, where ventricular asystole is usually at fault.[12,17]

In patients with complete A-V block, quinidine and Pronestyl have been shown to precipitate, or induce, the most serious prefibrillary mechanism disorders and ventricular fibrillation.[12,14,16] Quinidine and Pronestyl must therefore be avoided even when irregularities develop in the idioventricular rhythm.

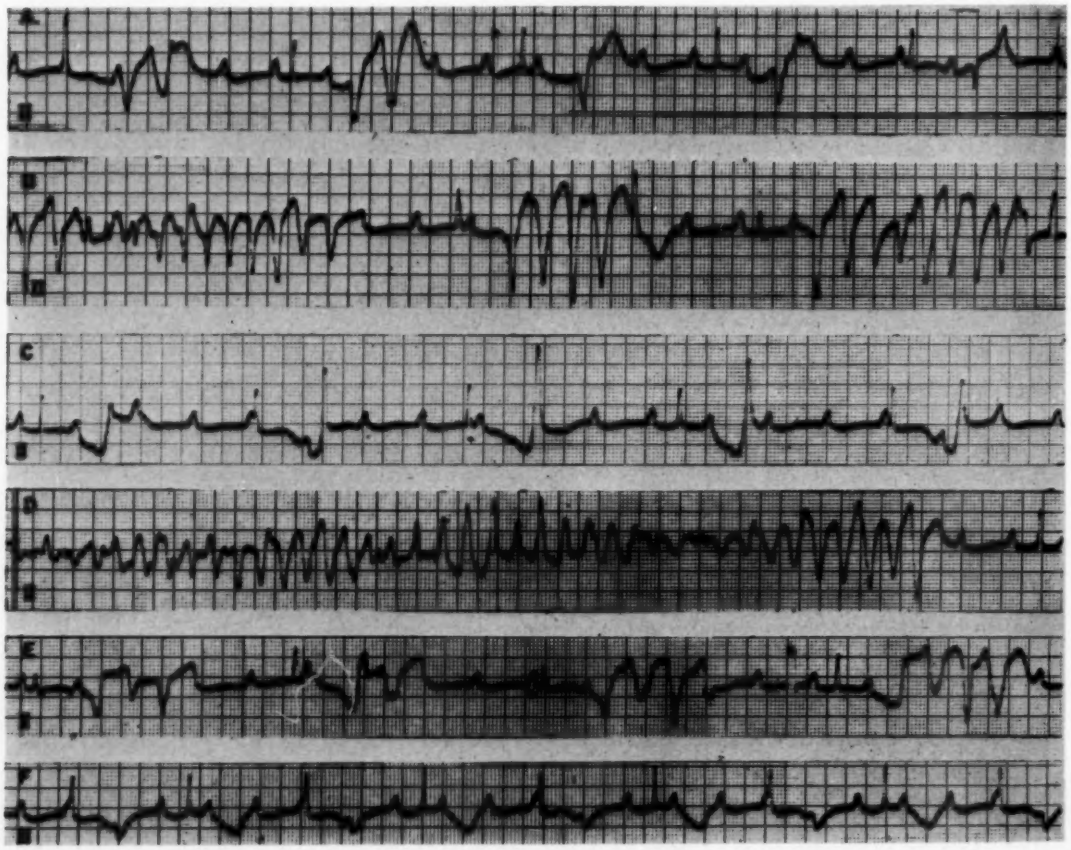

Fig. 5.—A 59-year-old woman who exhibited repeated syncopal and convulsive attacks resulting from ventricular acceleration. *A*, 13:30 P.M. admission, ECG showing complete heart block with a slow basic pacemaker and numerous ectopic beats, at times in runs of two. *B*, 3:30 P.M. Short bursts of ventricular tachycardia and prefibrillary mechanism following quinidine SO_4, 0.2 Gm., at 1:30 P.M. *C*, 5:30 P.M. Resumption of faster basic pacemaker with coupled ectopic beats following treatment with Ringer's lactate. *D*, 6:22 P.M. Ventricular fibrillation twelve minutes after beginning ⅙ M. sodium lactate. *E*, 7:00 P.M. Similar to control tracing after resumption of Ringer's lactate. *F*, 7:45 P.M. Forty-five minutes following Isuprel, 15 mg. sublingually, showing regular basic pacemaker of adequate rate with disappearance of ectopic foci.

In a single patient who exhibited myocardial irritability (Fig. 5), intravenous sodium lactate was strongly suspected of producing ventricular fibrillation. Further experience will be necessary to fully evaluate the effect of sodium lactate

in such situations. At present, Isuprel is accepted as the safest drug under such conditions, as well as being the most reliable stimulant of the higher idioventricular centers.

PROGNOSIS

The prognosis in patients with symptomatic A-V block is still rather poor. The average life expectancy is generally from three to four years. However, one of our patients who suffered syncopal attacks was observed over a period of fifteen years. With ventricular acceleration as the mechanism producing attacks, the outlook is distinctly less favorable.

SUMMARY

Complete heart block meeting our criteria is uncommon. Arteriosclerotic heart disease was the chief etiologic factor in 90 out of 49,000 patients on whom electrocardiographic studies were made. Overdigitalization was the most frequent toxic cause. The QRS configuration or duration is considered an unreliable index of the position of the pacemaker, since bundle branch block frequently may coexist with complete heart block. Isuprel (isopropyl norepinephrine) was found to be the most useful drug in our series, regardless of the underlying mechanism producing attacks. In only three of our patients was ventricular fibrillation considered the mechanism producing symptoms. The prognosis depends upon the stability of the idioventricular pacemaker, the presence of symptoms, and the underlying mechanism producing attacks. With some exceptions, however, the prognosis of symptomatic complete heart block is generally poor.

SUMMARIO IN INTERLINGUA

Complete bloco cardiac conforme a nostre criterios non es frequente. Morbo cardiac arteriosclerotic esseva le major factor etiologic in un gruppo de 90 tal patientes detegite inter 49.000 casos in que studios electrocardiographic esseva executate. Le plus frequente causa toxic esseva superdigitalisation. Le configuration o le duration de QRS non es considerate como un bon indicio del position del pacemaker, proque frequentemente bloco de branca pote coexister con complete bloco cardiac. Nos trovava que Isuprel (isopropylo-norepinephrina) esseva le plus utile droga empleate in nostre serie de casos, sin reguardo al mechanismo fundamental que produceva le attaccos. In solmente tres de nostre patientes il esseva considerate que fibrillation ventricular esseva le mechanismo que produceva le symptomas. Le prognose depende del stabilitate del pacemaker idioventricular, del presentia de symptomas, e del mechanismo fundamental que produce le attaccos. Nonobstante, con alicum exceptiones, le prognose de complete bloco cardiac symptomatic es generalmente pauco favorabile.

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THE GENESIS OF THE "PRESYSTOLIC" MURMUR IN MITRAL STENOSIS

HENRY T. NICHOLS, M.D., WILLIAM LIKOFF, M.D., HARRY GOLDBERG, M.D., AND MORTON FUCHS, M.D.

PHILADELPHIA, PA.

INTRODUCTION

SOUND is caused by vibratory motion. The heart vibrates during its dynamic function and theoretically each of its structural components is capable of producing sound. However, since oscillations arise and are transmitted from all cardiac areas almost simultaneously it is difficult to define the mechanism initiating the primary wave motion.

Until intracardiac surgery made such an inquiry possible the inability to make critical observations within the contracting human heart was a serious deterrent to the solution of this problem. Recently, utilizing the information obtained from the direct examination of functioning valves, the "sharp" first sound in mitral stenosis was attributed to the termination of the abrupt intra-atrial displacement of the leaflets at the time of closure.[1] This concept correlates the acoustic qualities of the sound with the physical state of the atrioventricular valve, its mechanical action, and the laws governing the intensity, pitch, and duration of sound.

Most cardiac murmurs are not as satisfactorily explained. Generally they have been considered to arise from vibrations created by the rapid, turbulent flow of blood across abnormal valve orifices. However, this view as it relates to the production of the "presystolic" murmur of mitral stenosis was placed in open question during the investigation into the genesis of the "sharp" first sound. The present report defines the basis of this doubt and presents a concept as to the genesis of the "presystolic" murmur which is consistent with the actual function of the stenotic mitral valve and the fundamental theories determining sound.

OBSERVATIONS

1. *The Mechanics of Valve Function.*—The mitral valve consists of a large anterior and smaller posterior cusp separated by two incisures in the antero-lateral and posteromedial positions above the respective chordae tendineae.

From the Departments of Medicine and Thoracic Surgery, Hahnemann Medical College and Hospital, Brith Sholom Cardiopulmonary Laboratory; and The Bailey Thoracic Clinic, Philadelphia, Pa.

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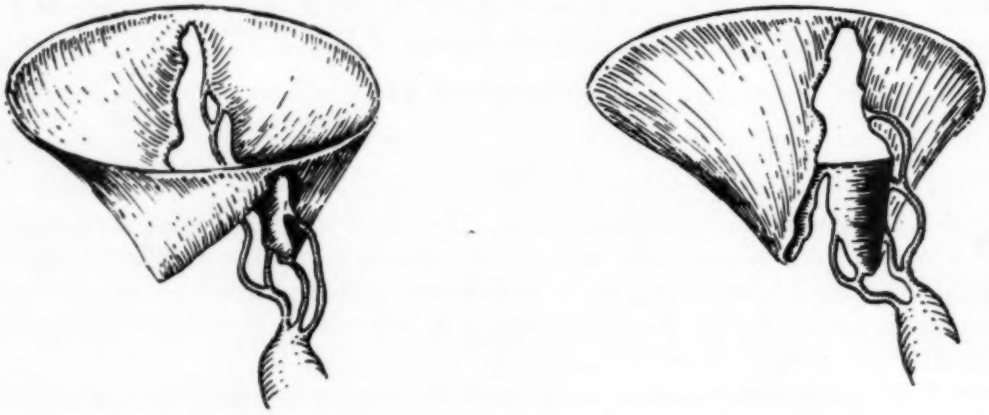
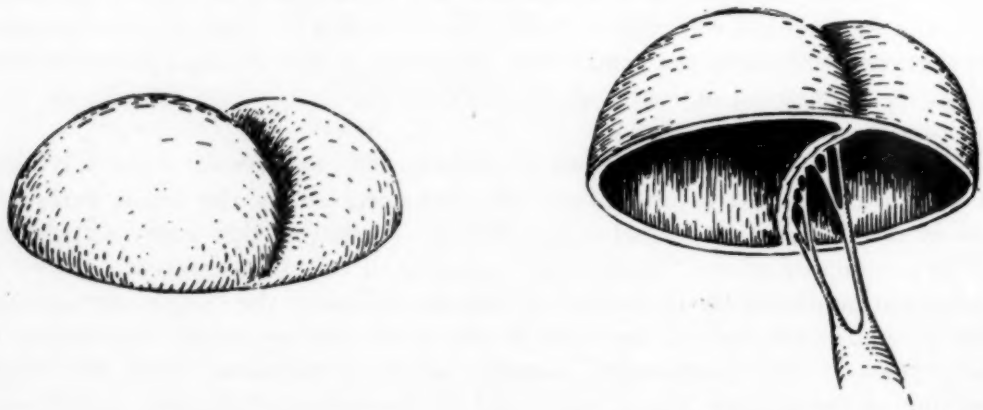
Since the incisures fall short of reaching the valve root by several millimeters a continuous rim of tissue is found at the periphery. The valve is supported by chordae tendineae which are more numerous along the free margins of the cusps and assure a firm coaptation of the edges along the Y-shaped line of closure.

In effect the entire structure resembles a sail tightly rigged at one circumference and held by loose, elastic lines at the other.



A. *B.*

Fig. 1.—Intraventricular displacement of mitral valve leaflets during opening of normal valve (*A*) viewed from atrial cavity and (*B*) viewed from ventricular cavity.



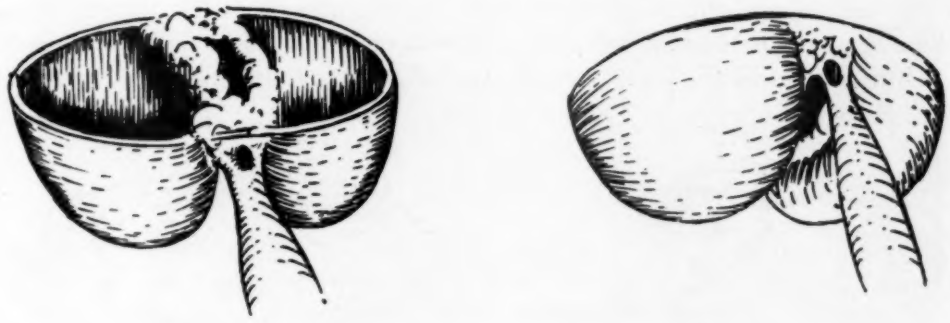
A. *B.*

Fig. 2.—Intra-atrial displacement of mitral valve leaflets during closure of normal valve (*A*) viewed from atrial surface and (*B*) viewed from ventricular surface.

Direct examination of the normal valve in the living patient is limited to events defined by the sense of touch. As they open the free edges appear to swing apart in a smooth arc until, at the completion of the action, each leaflet hangs equally depressed in the ventricular cavity. During closure the cusps gradually float upward until contact of the free edges is re-established. At this time the examiner can determine a gentle bulging of the central portion of each leaflet into the atrial cavity (Figs. 1 and 2). The closing action appears to be buffered by the restraining action of the elastic musculotendinous supporting structures.

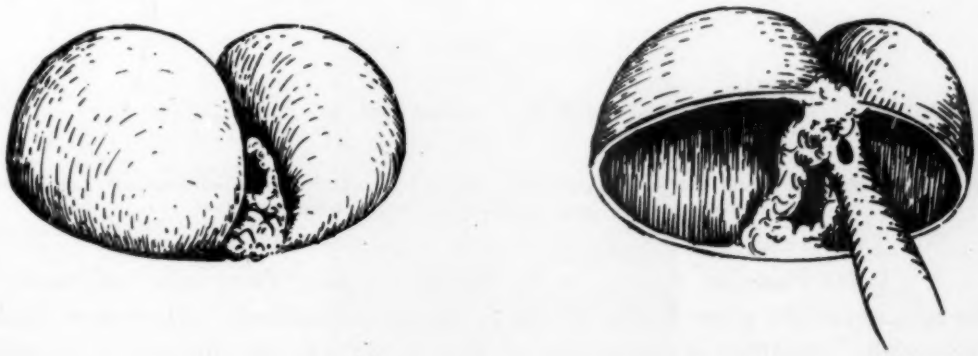
In significant mitral stenosis the leaflets are anchored at the atrioventricular ring and to a varying extent along the fused commissures. The proliferative tissue changes actually secure the free border of the cusps so that the structure now may be likened to a sail rigged throughout its entire circumference.

Direct examination of this type of valve discloses a marked alteration in its mechanical function. The edges of the cusps no longer are capable of freely swinging downward into the ventricular cavity during diastole. The extent of their limited separation determines the size of the mitral orifice. Since one of its



A. *B.*

Fig. 3.—Intraventricular displacement of mitral leaflets during opening of stenotic valve. *A*, Viewed from atrial surface. Note fixation of free edges of the leaflets. *B*, Viewed from ventricular surface.



A. *B.*

Fig. 4.—Intra-atrial balloonment of mitral leaflets during closure of stenotic valve (*A*) viewed from atrial surface and (*B*) viewed from ventricular surface.

borders is relatively fixed at the area of commissural fusion and the other at the annular ring the leaflet responds to the pressure exerted against its atrial surface by bulging downward at its central portion in a deep concave arc (Fig. 3).

As diastole continues and the atrium empties the atrial pressure decreases and higher pressures develop in the ventricle which reverse the direction of the leaflet balloonment and ultimately produces a rapid, forceful excursion of the flexible cusps into the atrium (Fig. 4). It is during the course of this displacement that the examiner defines a distinct vibration particularly over the septal leaflet which ends abruptly as the cusps attain full balloonment. The oscillation simulates the coarse ripple in a sail as it fills in response to a full gust of wind.

In extreme stenosis the leaflets are converted to firm, inflexible tissue by extensive fibrosis or depositions of calcium. The central portion of each cusp no longer can bulge in either direction and the valve functions as a flat disc with the degree of mobility entirely dependent upon the movement remaining at the free edges (Fig. 5).

The total experience gained by examining the functioning mitral valve suggests that stenosis alters the basic mechanism of leaflet displacement. When the free edges of the leaflets are fixed at the commissures, but the elasticity of the central portion is not compromised seriously the cusps respond by bulging into the ventricle as the valve opens and into the atrium at the time of closure. In the course of the abrupt intra-atrial displacement a gross vibration is palpable. However, when the leaflet is inelastic balloonment and associated vibrations are not observed.

A. *B.*

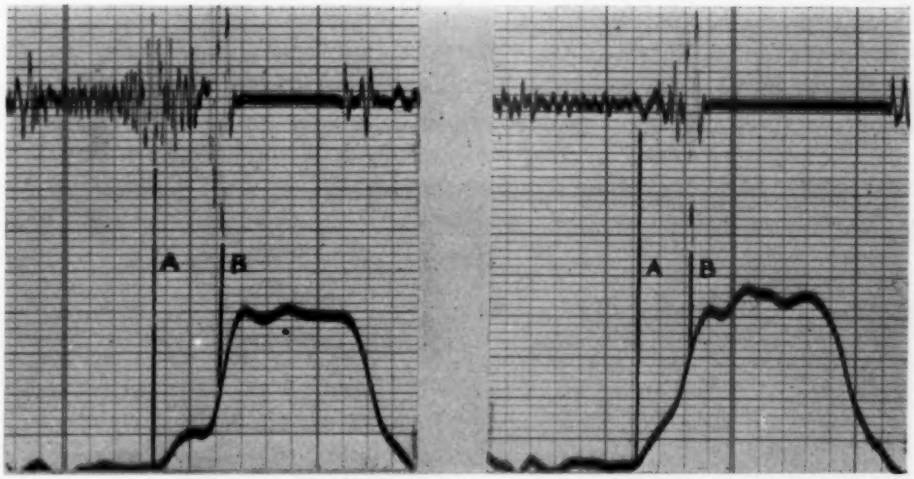
Fig. 5.—Flat disklike mitral valve during closure, indicating no intra-atrial balloonment, (*A*) viewed from atrial surface, and (*B*) viewed from ventricular surface.

2. *Valve Function Related to the Presence of the "Presystolic" Murmur.*— The relation of the gross leaflet vibration during intra-atrial displacement to the "presystolic" murmur was established by correlating the mechanics of valve function with the auscultatory findings noted prior to operation.

It has been a consistent experience that the vibration occurs only when a "presystolic" murmur is heard. The oscillation is not palpated in the presence of a mid-diastolic murmur alone. However, the latter is almost invariably accompanied by a localized diastolic thrill over the surface of the lateral border of the left ventricle. When this thrill is not discernible it very likely is directed into the central cavity of the ventricle or toward the interventricular septum where it cannot be felt. Both the vibration of the septal leaflet and the thrill over the lateral wall of the left ventricle are demonstrated when the "presystolic" and mid-diastolic murmurs are heard in the same patient.

In our experience the vibration and the "presystolic" murmur have not been encountered when extensive fibrosis or calcification of the leaflets or fusion and fixation of the musculotendinous supporting structures reduce the flexibility of the cusps to a point where the valve functions as a disc. However, these tissue changes do not interfere with the production of a mid-diastolic murmur.

When gentle finger pressure is exerted over the septal leaflet just as intra-atrial displacement takes place the vibration is obliterated. Recordings taken over the surface of the heart indicate the "presystolic" murmur likewise disappears. Fig. 6,*A* depicts the "presystolic" murmur in relation to the ventricular isometric period prior to the application of pressure over the vibrating septal leaflet.



A. *B*.

Fig. 6.—Modification of the presystolic murmur by obliteration of leaflet vibration. *A*, Murmur and vibration present. Onset (*A*), termination (*B*). *B*, Murmur and vibration eliminated by finger pressure on septal leaflet.

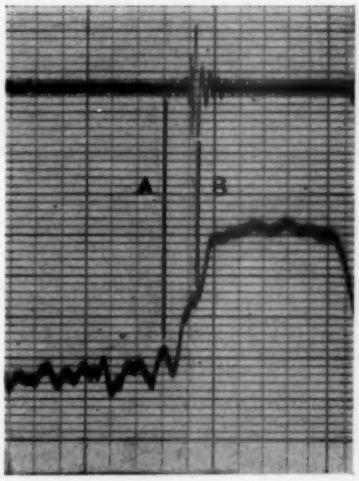


Fig. 7.—The position of the presystolic murmur in relation to the isometric period of the left ventricle obtained during left heart catheterization. *A*, Onset of murmur. *B*, Onset of "sharp" first heart sound.

Fig. 6,*B* indicates the disappearance of the murmur when the vibration is obliterated by stabilizing the septal leaflet with the finger so that it cannot complete its excursion into the atrium.

3. *The Position of the "Presystolic" Murmur in the Cardiac Cycle.*—The dynamic events within the right and left ventricles usually occur simultaneously.

Therefore, the time relation of the "presystolic" murmur to the ventricular isometric period may be determined by phonocardiographic registrations during right or left heart catheterization.

These records indicate the murmur originates during the first rise in ventricular pressure after the onset of the isometric period. Fig. 7 was obtained in a patient with a typical "presystolic" murmur. On direct examination the leaflet vibration was easily identified.

In contrast, Fig. 8 illustrates the initiation and termination of the mid-diastolic murmur prior to the onset of the isometric period. Direct examination of the valve failed to disclose leaflet vibration.

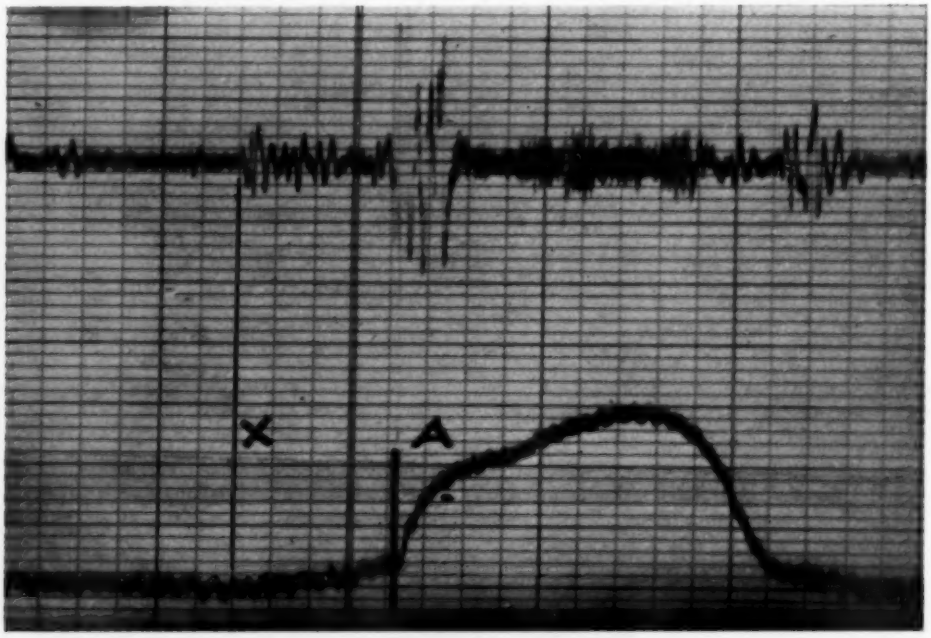


Fig. 8.—The appearance of the midlate diastolic murmur prior to the onset of ventricular isometric period (*X*). Note normal position of first sound (*A*). Record obtained following mitral commissurotomy. (Direct pressures).

4. *The Factors Related to the Acoustic Qualities of the "Presystolic" Murmur.*—Viewed as a source of sound the normal mitral valve is a stretched, two-dimensional membrane with one border mounted on an annular ring and the other supported by chordae tendineae but comparatively free. When such a structure vibrates the velocity of wave motion, which determines pitch, is mathematically related to the tension, mass, and length of the tissue and, of these, tension is most important.

The "presystolic" murmur is high in pitch and of varying duration. It has a crescendo quality and terminates in a "sharp" first sound. On the cardiospectogram the predominant frequency averages 300 cycles per minute and the intensity increases as the first sound is approached.[2] The "sharp" first sound is also high in pitch with an average frequency of 600 cycles per minute.

In contrast, the mid-diastolic murmur is a low-pitched decrescendo sound and the predominant frequency averages 100 cycles per minute.

According to the laws governing sound in a stretched, two-dimensional membrane, and in view of the acoustic qualities of the "presystolic" murmur and the "sharp" first sound both of these auscultatory events should be produced when the tension of the vibrating source is increased, and the mass and length decreased. Direct examination of the valve suggests these conditions exist as the cusps are displaced into the atrium. This movement occurs abruptly and with great vigor, as if the available area of valve tissue is under great tension and the restraining action of the musculotendinous structure has been increased. In brief, the vibration responsible for the "presystolic" murmur appears to develop when leaflets are significantly stretched and taut.

In keeping with the previous considerations the mid-diastolic murmur should be produced when the tension of the vibrating source and its mass and length are comparatively more normal. Although the genesis of the murmur has not been determined the conditions for its production appear to be satisfied only when the cusps are displaced intraventricularly during diastole. Although the balloonment is distinct at this time, it is not abrupt and is not opposed by the action of the chordae tendineae.

DISCUSSION

When the stenotic atrioventricular cusps retain a critical degree of flexibility they are forcefully displaced into the atrium during valve closure and produce a palpable vibration. The constant, exclusive association of this oscillation with the "presystolic" murmur forms the basis for a reconsideration of the genesis of the murmur and its position in the cardiac cycle.

The present concept contrasts sharply with classic views relating the "presystolic" murmur to the turbulence of blood flow across the mitral orifice during atrial contraction. Fundamentally it attributes the murmur to leaflet vibrations arising from the force exerted against the cusps by the increasing ventricular pressure during the isometric period. Thus the murmur is considered systolic in time.

The initial ventricular displacement of the central portions of the stenotic, flexible mitral leaflets as the valve opens develops in response to the increased pressure exercised against the atrial surface of the cusps. This pressure falls as diastole continues and is succeeded by a rapidly developing intraventricular force which reverses the leaflet bulge and produces a forceful intra-atrial balloonment. Although it is logical to assume vibrations are produced during the entire valve action these are not palpable or intense enough to create sound until the intra-atrial displacement takes place.

The palpable vibration, initiated during the actual intra-atrial balloonment, is responsible for the "presystolic" murmur. A succeeding oscillation arises at the very instant the displacement is abruptly concluded and results in the "sharp" first sound.

The appearance of the "presystolic" murmur prior to the "sharp" first sound is not inconsistent with the view which maintains the murmur occurs in systole.

The normal first sound, derived from vibrations arising with the buffered, gentle intra-atrial leaflet displacement at the time of valve closure, occurs at the onset of the ventricular isometric period and differentiates mechanical diastole

from systole. However, in mitral stenosis the intra-atrial balloonment is altered by an increased resistance of the cusps and significant opposing pressures within the atrium. Because of these physical and dynamic deviations the intra-atrial displacement is abrupt and delayed until after the ventricular isometric period or mechanical systole has been initiated. Since the short, high-pitched or "sharp" first sound is produced by the termination of this abnormal balloonment, it no longer signifies the onset of mechanical systole. If an auscultatory event such as the "presystolic" murmur immediately precedes the "sharp" first sound it too may still arise in systole.

In spite of the evidence confirming the systolic occurrence of the "presystolic" murmur no practical gain results from a redesignation of the present accepted nomenclature.

During their displacement into the atrium by the rising force within the ventricle, the stenotic atrioventricular leaflets appear to be placed under abnormal tension. This results from the proliferative tissue changes which decrease the mass and length of the cusps by the restraining action of the scarred, foreshortened musculotendinous structures, and by the opposing abnormal atrial pressures. In keeping with the acoustic laws governing sound production in a stretched, two-dimensional membrane, the increased tension adequately accounts for the high pitch of the "presystolic" murmur. The similarity in the characteristics of the "sharp" first sound and the murmur is attributed to the fact that both events arise during a single mechanical action with the leaflets under increased tension. In contrast, the acoustic qualities of the mid-diastolic murmur imply it arises during a different phase of valve action or through an independent mechanism.

If atrial contraction is not intimately concerned with the genesis of the "presystolic" murmur, the question immediately arises as to the disappearance of the murmur with the onset of fibrillation.

It is reasonable to assume the intraventricular leaflet displacement is more exaggerated by atrial contractions than by fibrillary movements. Hence less force is necessary to reverse balloonment during fibrillation and, generally, its magnitude is insufficient to establish vibrations from which the "presystolic" murmur develops.

Occasionally a "presystolic" murmur is heard during atrial fibrillation when diastole is exceptionally short. This may develop because the ventricular displacement of the leaflets is greater in the early rather than late phase of diastole, particularly when the intra-atrial pressure is markedly elevated. Thus the more dependent position of the cusps at the onset of ventricular systole simulates the conditions leading to the "presystolic" murmur when atrial contraction occurs.

A review of all the considerations in this study suggests the presence of a "presystolic" murmur fundamentally depends upon the physical state of the stenotic valve. The murmur cannot be produced unless the central portions of the leaflets remain flexible. The immobile or completely calcified valve is not characterized by this murmur because the leaflets cannot be displaced abruptly into the atrium during closure. Since the mitral orifice may be more severely compromised in an immobile than in a flexible valve, it is obvious the "presystolic" murmur does not necessarily indicate the most advanced degree of mechanical obstruction. On the other hand the common tendency to accept the murmur as a priori evidence of a "tight" mitral stenosis is reasonably correct·

Barring changes in rhythm the disappearance of a "presystolic" murmur may be attributed only to increasing fibrosis or calcification which renders the leaflets inflexible. Most probably under these circumstances the mitral orifice is reduced further in size.

CONCLUSIONS

1. The total experience gained by examining the functioning mitral valve suggests that stenosis alters the basic mechanism of intra-atrial leaflet displacement at the time of valve closure.

2. When the free edges of the leaflets are fixed at the commissures but the elasticity of the central portion is not compromised, a gross vibration is palpable during intra-atrial displacement.

3. It has been a consistent experience that this gross vibration occurs only in those patients in whom a presystolic murmur is heard.

4. When the leaflets are inelastic intra-atrial balloonment and associated vibrations are not observed. These patients do not have a presystolic murmur.

5. Phonocardiographic registrations during right or left heart catheterization reveal the "presystolic" murmur originates during the first rise in ventricular pressure after the onset of the isometric period. The murmur therefore is considered systolic in time.

6. The present concept as to the genesis of the presystolic murmur is consistent with the acoustic qualities and the theoretical factors related to the intensity, pitch, and duration of sound in a stretched two-dimensional membrane.

CONCLUSIONES IN INTERLINGUA

1. Le summa del experientias ganiate per le examination del valvula mitral in function suggere que stenosis altera le mechanismo fundamental del displaciamento del foliolos intra-atrial al tempore del clausura del valvula.

2. Quando le libere bordos del foliolos es fixate al commissuras sed le elasticitate del portion central non es compromittite, un grosse vibration es palpabile durante le displaciamento intra-atrial.

3. Il ha essite regularmente nostre experientia que iste grosse vibration occurre solmente in ille patientes in qui es audite un murmure presystolic.

4. Quando le foliolos es inelastic, le ballonamento intra-atrial con su associate vibrationes non es observate. Iste patientes ha nulle murmure presystolic.

5. Registrationes phonocardiographic durante catheterisation del corde sinistre o dextere revela que le murmure presystolic ha su origine durante le prime elevation in le pression ventricular post le initio del periodo isometric. Consequentemente le murmure es considerate como systolic quanto al tempore de su occurrentia.

6. Le presente concepto in re le genese del murmure presystolic es compatibile con le characteristicas acustic e con le factores theoric pertinente al intensitate, altor, e duration del sono in un tendite membrana bidimensional.

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SELECTED QUANTITATIVE APPLICATIONS OF DIGITAL RHEOPLETHYSMOGRAPHY

G. E. Burch, M.D.

New Orleans, La.

THE digital rheoplethysmogram consists of continuous curves of the time course of volumes, rates, and accelerations in inflow, outflow, and differences between inflow and outflow in the digit during a single pulse cycle.[1-3] These curves lend themselves to various quantitative analyses, which reveal aspects of the peripheral circulation not evident from noncontinuous curves and permit certain observations of normal and abnormal physiologic states of the central and peripheral circulation. Selected disease states are presented merely to illustrate differences between normal and abnormal physiologic phenomena and to show how selected quantitative analyses can be employed to describe aspects of the time course of digital blood flow. No effort is made at this time to define the extent of variations in these values for the normal or any abnormal state or to explain differences noted. The same types of recordings and analyses are applicable to other organs by proper modification of the rheoplethysmograph.

MATERIALS AND METHODS

More than 300 digital rheoplethysmographic recordings were obtained on ten subjects, varying in age from 27 to 65 years. Four were normal, two had aortic insufficiency, one Raynaud's disease, one congestive heart failure due to hypertension, one Leriche's syndrome, and one Takayasu's syndrome (pulseless disease) (Table I).[4,5] The subjects rested in a hospital-type bed in a comfortable, air-conditioned observation room (75° F., 60 per cent relative humidity) with the second right finger tip (2RF) and third right finger tip (3RF) passively supported at heart level. The total digital volume, digital bone volume, soft tissue volume, average resting volume of blood contained within the digital vascular bed, and digital surface area were calculated by methods previously described.[1-3] Various conditions and stimuli were employed as described hereafter. Details of these procedures and the methods of analysis of the records have been described previously.[1-3]

From the Department of Medicine, Tulane University School of Medicine and Charity Hospital of Louisiana at New Orleans.

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TABLE I. COMPARISON OF DIGITAL VOLUME OF FINGER TIP, SOFT TISSUE, AND BONE IN TEN SUBJECTS STUDIED

SUBJECT NO.	CLINICAL STATE	AGE (YEARS)	SEX	COLOR	BLOOD PRESSURE	DIGITAL VOLUME			SURFACE AREA OF FINGER TIP (CM.^{2})
						FINGER OR TOE* (C.C.)	SOFT TISSUE (C.C.)	BONE	
1	Normal	28	M	W	128/76	5.490	4.617	0.873	13.16
2	Normal	27	F	W	107/70	3.670	3.141	0.529	10.05
3	Normal	32	F	W	130/80	3.600	3.085	0.515	9.93
4	Congestive heart failure	56	M	C	178/96	7.050	5.883	1.167	15.83
5	Aortic insufficiency	51	F	C	160/35	3.540	3.036	0.504	9.82
6	Raynaud's disease	47	M	W	120/80	4.600	3.896	0.704	11.64
7	Leriche's syndrome	65	M	W	138/80	4.200	3.571	0.629	10.95
8	Normal	30	M	W	100/66	5.450	4.585	0.865	13.09
9	Aortic insufficiency	48	M	W	228/0	5.700	4.788	0.912	13.52
10	Takayasu's syndrome	46	F	W	140/70	3.500	3.004	0.496	9.76

*2RF was studied in all subjects except No. 7, in whom 2LT was studied.

THEORETIC CONSIDERATIONS, RESULTS, AND ANALYSES

Time Course of Volume of Inflow, Outflow, and Difference Between Volume Inflow and Outflow.—The volume rheoplethysmograms (R_V), that is, the curves of the volume-time course of inflow (I_V), outflow (O_V), and difference between I_V and O_V (D_V), are shown for 2RF at heart level for a representative normal subject in a comfortable environment (Fig. 1), with the hand in a chamber of cold air (Fig. 2), before and after deep inspiration (Figs. 3 and 4), in a hot and humid environment (Fig. 5), and before and after norepinephrine (Figs. 6 and 7); for a subject with severe congestive heart failure before and after hexamethonium (Figs. 8 and 9); for a subject with severe aortic valvular insufficiency (Fig. 10); for a subject with Raynaud's disease (Fig. 11); and for the second right toe (2RT) of a subject with Leriche's syndrome before and after aortic bifurcation graft* (Figs. 12 and 13). A study of these representative curves reveals the various characteristics and differences among the rheoplethysmograms. The original traces have been omitted in order to save space.

Time Course of Digital Rate of Inflow, Outflow, and Difference Between Rates of Inflow and Outflow.—The rheoplethysmograms of rate (R_R), i.e., the rates of inflow (I_R), outflow (O_R), and difference between the rates of inflow and outflow (D_R) derived from the respective R_V curves are shown in Figs. 1 through 13. These rate curves represent the time course of the first derivatives of the volume curves.[1-3] Although differences among these various curves are evident on study of these, the R_V and R_R curves are presented primarily to make possible the presentation of the analyses and discussions to follow.

Time Course of Percentage Total Volume Inflow and Outflow per Pulse Cycle.—The R_V curves (volume curves of the rheoplethysmogram) may be expressed as the time courses of the percentage total inflow and outflow per pulse cycle by reference to the absolute ordinate percentages at the right of the graph (Figs. 1 to 13). Although it is not possible or necessary to describe the characteristics for each of the physiologic states presented, certain aspects are worthy of comment. For example, 47.4 per cent of the total *inflow* occurred during the systolic phase of the pulse cycle of the normal subject at rest in a comfortable environment, with a mean systolic rate of 58.9 cu. mm. per 5 c.c. part per second, whereas the remaining 52.1 per cent occurred during the diastolic

*Operation performed by Drs. M. E. DeBakey and Oscar Creech, Department of Surgery, Baylor Medical School, Houston, Tex.

TABLE II. CERTAIN QUANTITATIVE ANALYSES OF THE RHEOPLETHYSMOGRAM IN NORMAL AND ABNORMAL STATES

SUBJECT NO.	PHASE OF PULSE CYCLE	PHYSIOLOGIC OR CLINICAL STATE	DURATION (SEC.)	INFLOW		OUTFLOW		I_R/O_R
				% TOTAL I_V	MEAN RATE (CU. MM./ 5 C.C. PART/SEC.)	% TOTAL O_V	MEAN RATE (CU. MM./ 5 C.C. PART/SEC.)	
1	Systole	Normal	0.28	47.4	58.9	39.6	49.3	1.2
	Diastole		0.64	52.6	28.6	60.4	32.8	0.9
1	Systole	Normal, hand in chamber of cold air	0.26	62.9	7.5	38.7	4.6	1.6
	Diastole		0.58	37.1	2.0	61.3	3.3	0.6
2	Systole	Normal	0.35	74.2	91.4	61.3	75.7	1.2
	Diastole		0.45	25.8	24.9	38.7	37.1	0.7
	Systole	Normal, deep inspiration	0.32	52.7	35.9	40.8	27.8	1.3
	Diastole		0.64	47.3	16.1	59.2	20.2	0.8
	Systole	Normal, hot and humid environment	0.34	54.5	91.8	45.2	76.2	1.2
	Diastole		0.50	45.5	52.2	54.8	62.8	0.8
3	Systole	Normal	0.35	61.0	63.1	47.8	49.4	1.3
	Diastole		0.65	39.0	21.7	52.2	29.1	0.7
	Systole	Normal, after norepinephrine	0.36	57.9	37.2	39.6	25.5	1.5
	Diastole		0.79	42.1	12.4	60.4	17.7	0.7
4	Systole	Congestive heart failure	0.14	66.7	1.4			
	Diastole		0.54	33.3	0.2			
	Systole	Congestive heart failure, after hexamethonium	0.29	63.8	15.2	34.8	8.3	1.8
	Diastole		0.47	36.2	5.3	65.2	9.6	0.6

phase, which lasted 2.3 times longer for a mean rate of 28.6 cu. mm. per 5 c.c. part per second during the diastolic phase of the pulse cycle (Fig. 1). Forty per cent of the volume of outflow occurred during the systolic phase of the pulse cycle (mean rate 49.3 cu. mm. per 5 c.c. part per second); the remaining 60 per cent of the total outflow occurred during the diastolic phase of the pulse cycle, for a mean rate of 32.8 cu. mm. per 5 c.c. part per second (Table II). Thus, a large amount of blood flowed out of the normal digit during the systolic phase of the pulse cycle, although the rate of inflow was greater during the systolic phase than during the diastolic phase and outflow was greater during the diastolic phase of the pulse cycle.

Additional quantitative rheoplethysmographic data are summarized in Table II for the subjects selected for presentation. For the cardiac rate and other conditions of study, the subject with aortic insufficiency had a higher rate of outflow during the systolic phase of the pulse cycle than during the diastolic phase, even though there was an initial lag in outflow when compared

TABLE II.—CONT'D

SUBJECT NO.	PHASE OF PULSE CYCLE	PHYSIOLOGIC OR CLINICAL STATE	DURATION (SEC.)	INFLOW		OUTFLOW		I_R/O_R
				% TOTAL I_V	MEAN RATE (CU. MM./ 5 C.C. PART/SEC.)	% TOTAL O_V	MEAN RATE (CU. MM./ 5 C.C. PART/SEC.)	
5	Systole	Aortic insufficiency	0.36	89.7	97.2	61.5	66.7	1.5
	Diastole		0.48	10.3	8.3	38.5	31.3	0.3
6	Systole	Raynaud's disease	0.27	57.3	20.0	37.0	12.9	1.6
	Diastole		0.48	42.7	8.3	63.0	12.3	0.7
7	Systole	Leriche's syndrome	0.22	46.2	5.5	21.2	2.5	2.2
	Diastole		0.50	53.8	2.8	78.8	4.1	0.7
	Systole	Leriche's syndrome, after aortic graft	0.35	80.0	37.4	63.6	29.7	1.3
	Diastole		0.37	20.0	8.9	36.4	16.2	0.5
8	Systole	Normal	0.26	71.0	86.5	56.8	69.2	1.3
	Diastole		0.42	29.0	21.9	43.2	32.6	0.7
9	Systole	Aortic insufficiency	0.36	91.3	73.1	56.6	45.3	1.6
	Diastole		0.64	8.7	3.9+	43.4	19.5+	0.2
10	Systole	Takayasu's syndrome	0.32	63.5	58.1	50.2	45.9	1.3
	Diastole		0.48	36.5	22.3	49.8	30.4	0.7
	Systole		0.32	53.8	13.4	41.3	10.3	1.3
		Takayasu's syndrome, after norepinephrine	0.52	46.2	7.1	58.7	9.0	0.8

with inflow (Fig. 10).[6] For example, the rate of inflow was also exceedingly low during diastole in comparison with normal subjects.

Comment.—The presentation of the R_V curves in terms of percentages simplifies a comparison of the relative proportions of total digital inflow (I_V) and outflow (O_V) for any segment of the pulse cycle. These percentile relations vary with physiologic and disease states of the circulation, as shown in these illustrations. The mechanistic interpretation of variations and differences among digits remains to be determined.

Time Course of Inflow Remaining as Percentage of Blood Flowing in at any Moment in the Pulse Cycle.—The percentage of accumulated inflowing blood that remained in the digit at any given moment in the pulse cycle was obtained at .04- or .05-second intervals from the expression:

$$\frac{I_{V_t} - O_{V_t}}{I_{V_t}} \times 100 = \frac{D_{V_t}}{I_{V_t}} \times 100, \qquad (1)$$

where I_{V_t} and O_{V_t} represent the accumulated volume of inflow and outflow, respectively, in cubic millimeters per 5 c.c. part at time t (Figs. 1 to 13).

Comment.—It is evident from the graphs that the percentage remaining is higher during the early portion of the pulse cycle, reaching 100 per cent in the normal subject's hand in the cold atmosphere (Fig. 2) and in the subject with aortic insufficiency (Fig. 10), as compared with 58 per cent (Fig. 1) for the same moment in the pulse cycle when the normal subject rested in a comfortable environment. Lag in O_V was, therefore, increased by the cold. These graphs

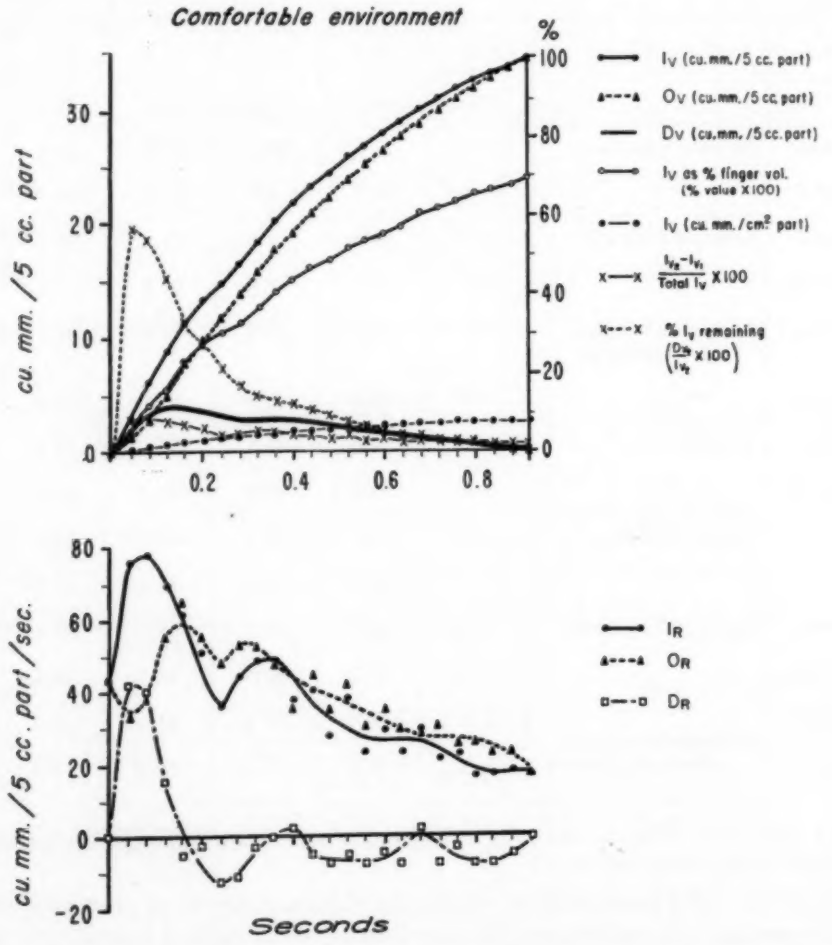

Fig. 1.—Various simultaneous rheoplethysmographic curves for a single pulse cycle for the second right finger tip (2RF) of a normal adult subject (No. 1) resting supine in bed in a comfortable room atmosphere with the digit at heart level. The ordinate at the left also represents cu. mm./cm.² of surface area of the digit. These conditions hold for all illustrations to follow unless otherwise indicated.

may be considered to reflect readily the moment-to-moment lag in outflow with respect to inflow. The lag in outflow must have been due to vasoconstriction, i.e., arteriolar constriction, which reduced the rate of flow into the venous side of the digital circulation from the arterial side, and constriction in the vessels distal to the arterioles with resultant delay in flow out of the digits themselves. These delays could be explained by the critical closing and opening phenomena[7-9] because digital vascular tone was high and the vessels were constricted in a cold

environment so that the lower arterial pressures during the diastolic phases of the pulse cycle would be insufficient to keep many of the vessels open.

The subject with aortic insufficiency and high pulse pressure also retained 100 per cent inflowing blood during the early phases of the pulse cycle (Fig. 10). This again may be an expression of the critical closing and opening phenomena of Burton. In this subject (blood pressure 186/0) and in others described in detail elsewhere,[4,5] closure of many of the digital vessels may have readily occurred when the diastolic pressure fell to low levels, approaching 0 mm. Hg. The increase in tone on the venous side of the digital circulation[4,5] may also have contributed to the lag in outflow early in the pulse cycle. The configuration of the trace of the subject with Raynaud's disease (Fig. 11) did not differ greatly from that of the normal, even though the volumes and rates of flow were low.

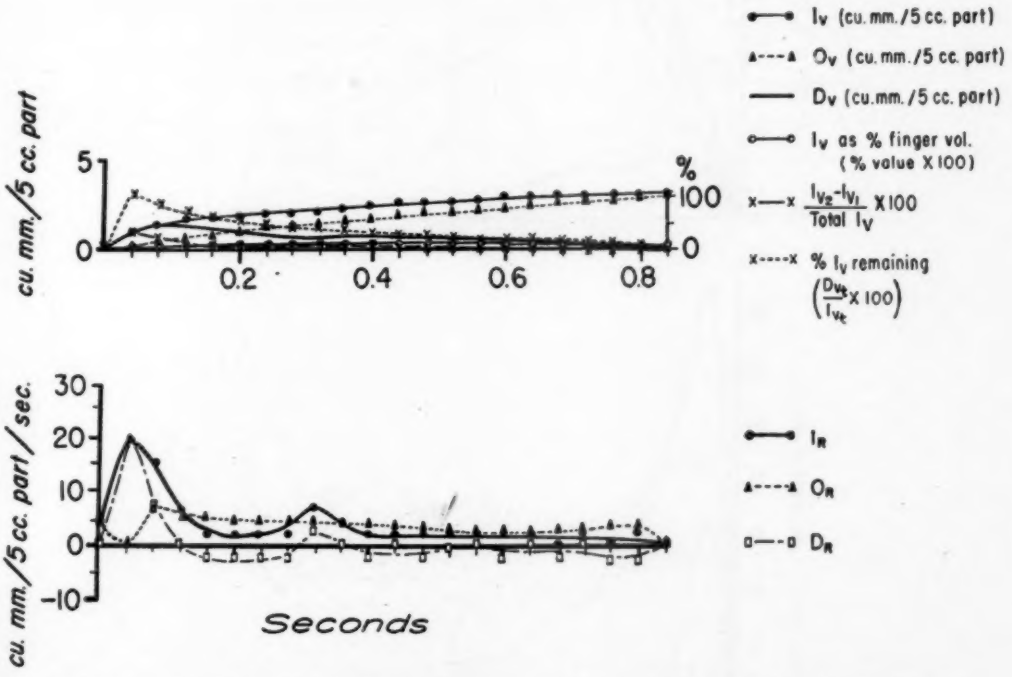

Fig. 2.—Various simultaneous rheoplethysmographic curves for the same subject of Fig. 1, but with the right hand in a chamber of cold air (1°C).

Even if his digital tone had been high, the sclerodermatous tissue would have interfered with "critical" closure of the vessels during the diastolic interval. However, it is more likely that vascular tone was not high at the time of observation.

Variations in the percentage of blood remaining in the digit for the different physiologic states studied (Figs. 1 to 13) reflect fluctuations in rates of ejection by the left ventricle, as well as the state of the arterial system, arterioles, and more distal vessels. Obviously, the more rapid the onset and the greater the volume of outflow, the smaller will be the percentage of inflowing blood remaining. These curves, like the D_V curves, are expressions of the time course of

digital vascular distention but not necessarily an index of distensibility, because of other unknown variables. Had the intravascular pressures been recorded, aspects of the distensibility and "elasticity" of the vascular bed as a whole could have been more accurately evaluated. If these recorded curves were such an index, then the digits of the subject with Raynaud's disease (Fig. 8) indicate even greater distensibility for the vascular bed than in the normal subject (Fig. 1).

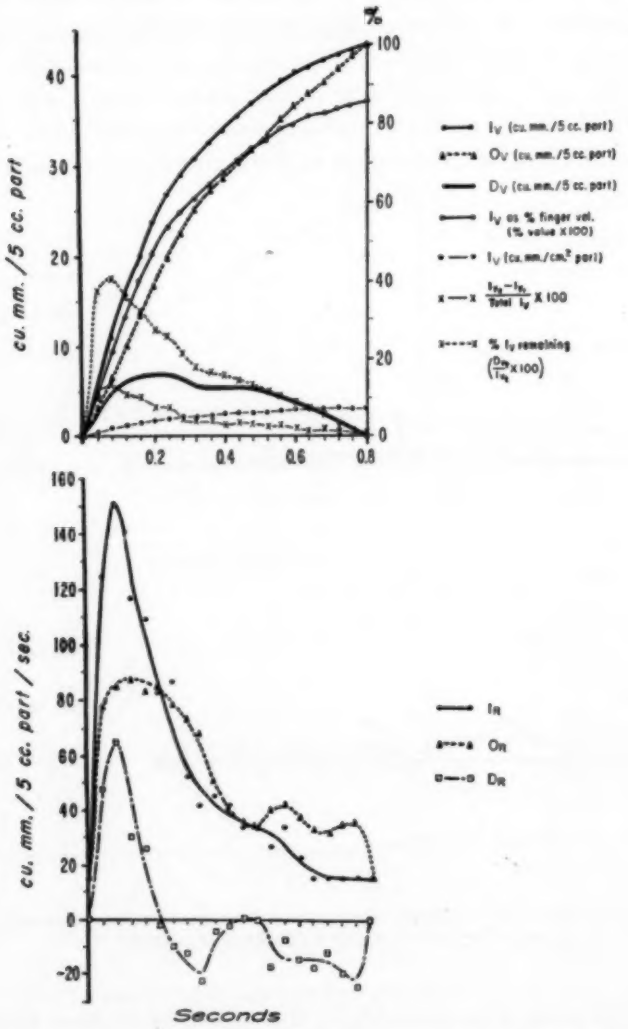

Fig. 3.—Various simultaneous rheoplethysmographic curves for a normal adult subject (No. 2) resting quietly in a comfortable room atmosphere.

This is not necessarily true, because this subject had sclerodermatous changes with fairly rigid digital tissues. The percentage of inflow remaining may have been high, but the volumes involved were small. The absolute quantities must be considered when such curves are being evaluated.

These curves also serve as an index of the quantity of inflowing blood that remains for local chemical exchange with the tissues. For example, the subject with Raynaud's disease had a low quantity of blood flow, but the digits seemed to retain a fairly high percentage of the inflowing blood for purposes of chemical exchange.

It should be noted that the rheoplethysmogram (RPG) does not differentiate between freshly inflowing blood and blood that may already have been in the digit and is merely displaced onward in the fingertip by the incoming blood. This differentiation would be necessary in order to determine more precisely how long the blood actually remains in the part.

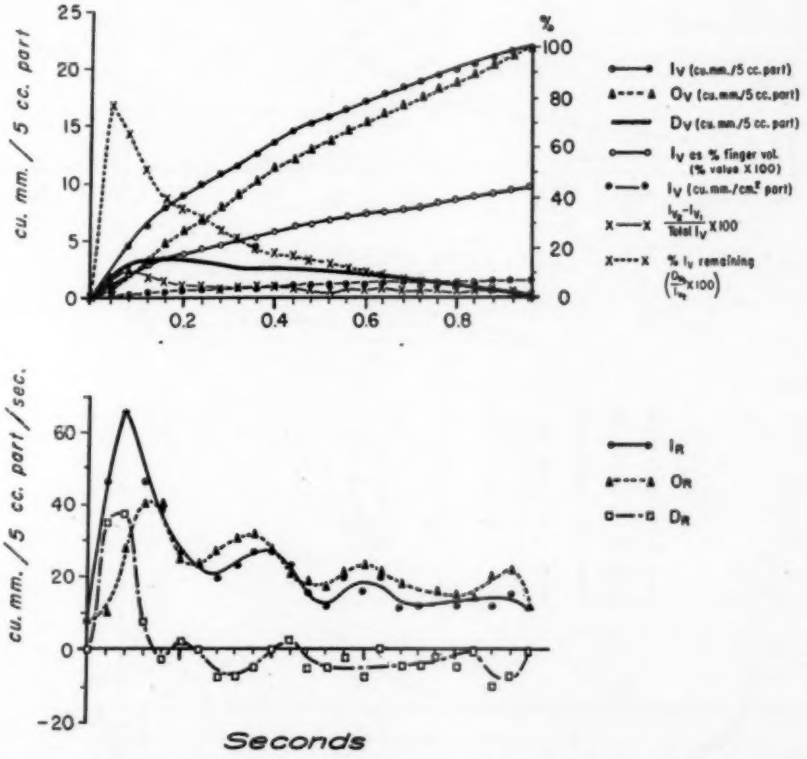

Fig. 4.—Various simultaneous rheoplethysmographic curves for the same normal adult subject of Fig. 3 during the state of vasoconstriction produced by deep inspiration.

Time Course of Inflow Remaining at Any Point in the Pulse Cycle as Percentage of Total Inflow.—The time course of accumulated blood that remained in the digit up to a certain moment as a percentage of the total inflow into the finger tip during the entire pulse cycle was determined by calculating the following values at each 0.04-second interval during a single pulse cycle:

$$\frac{I_{V_t} - O_{V_t}}{\text{Total } I_V} \times 100 = \frac{D_{V_t}}{\text{Total } I_V} \times 100, \qquad (2$$

where I_{V_t} and O_{V_t} represent the accumulated volumes of inflow and outflow, respectively, in cubic millimeters per 5 c.c. part at time t in the pulse cycle and total I_V, the total volume of blood that flowed into the digit during the entire pulse cycle.

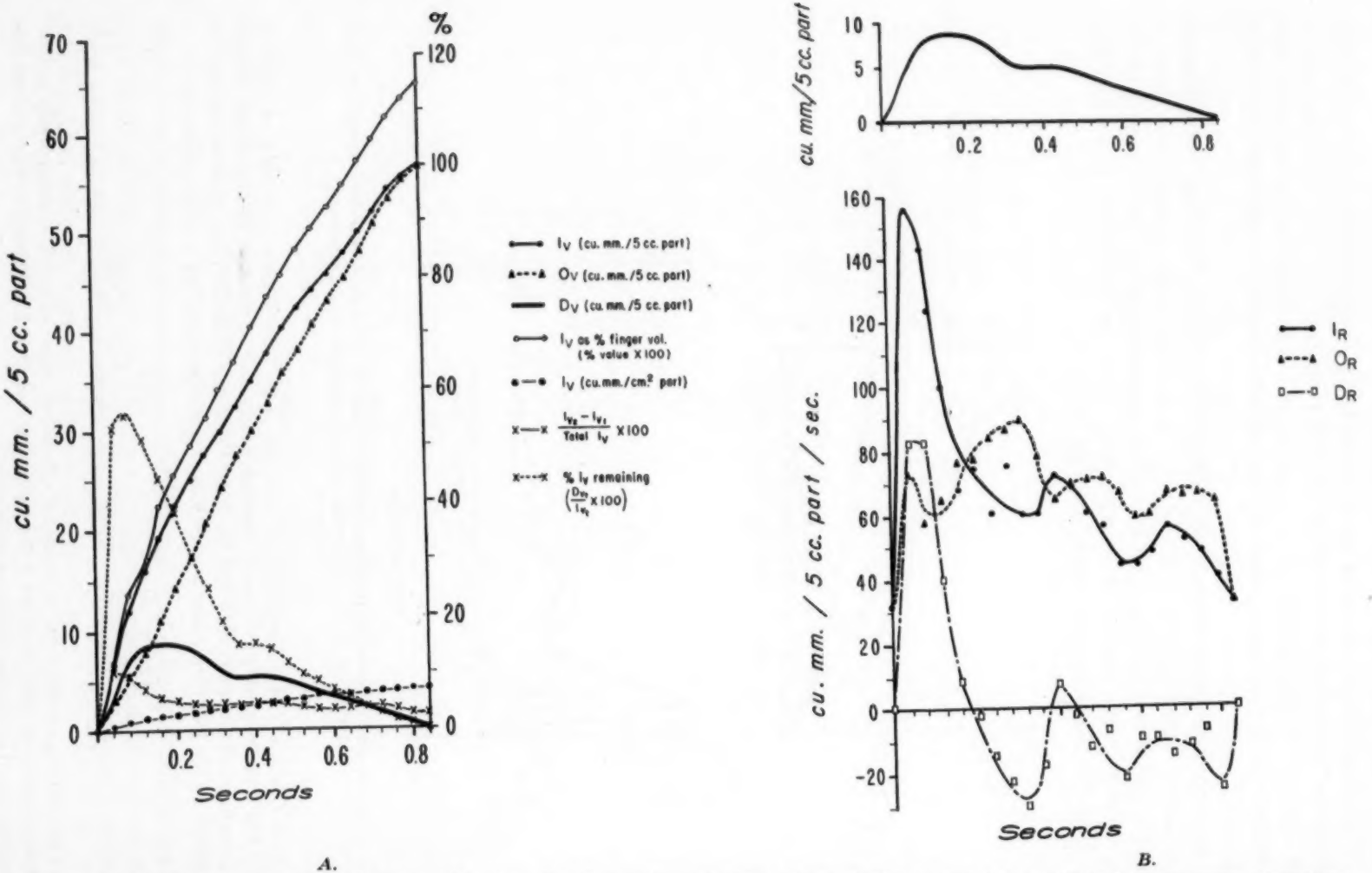

Fig. 5.—Various simultaneous rheoplethysmographic curves for the same normal adult subject of Figs. 3 and 4 in a hot and humid room atmosphere (temperature 38° C., relative humidity 38 per cent).

Comment.—The curves for the different physiologic states varied in a manner like the volume pulse wave, since they are the volume pulse waves divided by a constant, the total inflow for that pulse cycle. These curves are not illustrated but can readily be calculated from the D_V curves and the total inflow values shown in the respective figures. Thus, curves of magnitudes less than the volume pulse wave, D_V, can be produced either by a reduction in the amount of inflowing blood remaining in the digit or by an increase in total inflow, whereas curves of magni-

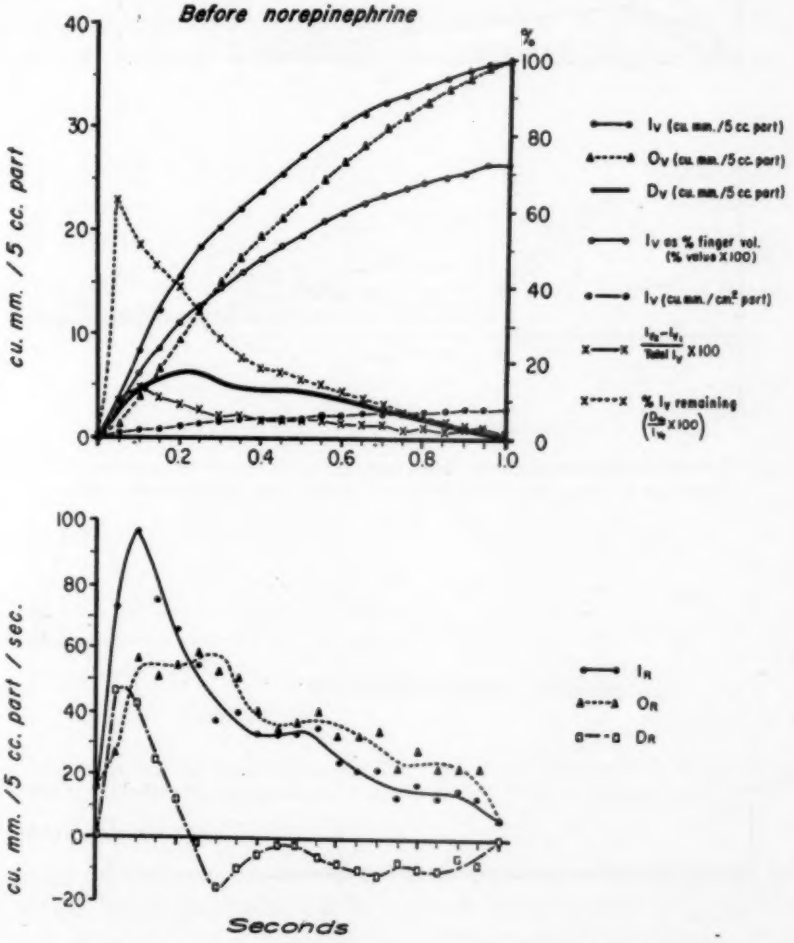

Fig. 6.—Various simultaneous rheoplethysmographic curves of a normal subject (No. 3) resting in a comfortable room atmosphere.

tudes greater than D_V can be produced either by an increase in the amount of inflowing blood remaining in the digit or by a reduction in total volume of digital inflow. The interrelations of these variables are influenced by the physiologic state of the central, general, and local portions of the cardiovascular system.

The Time Course of the Change in Volume Inflow as Percentage of Total Volume Inflow.—For a temporal description the variations in volume inflow as a percentage of total inflow, values were

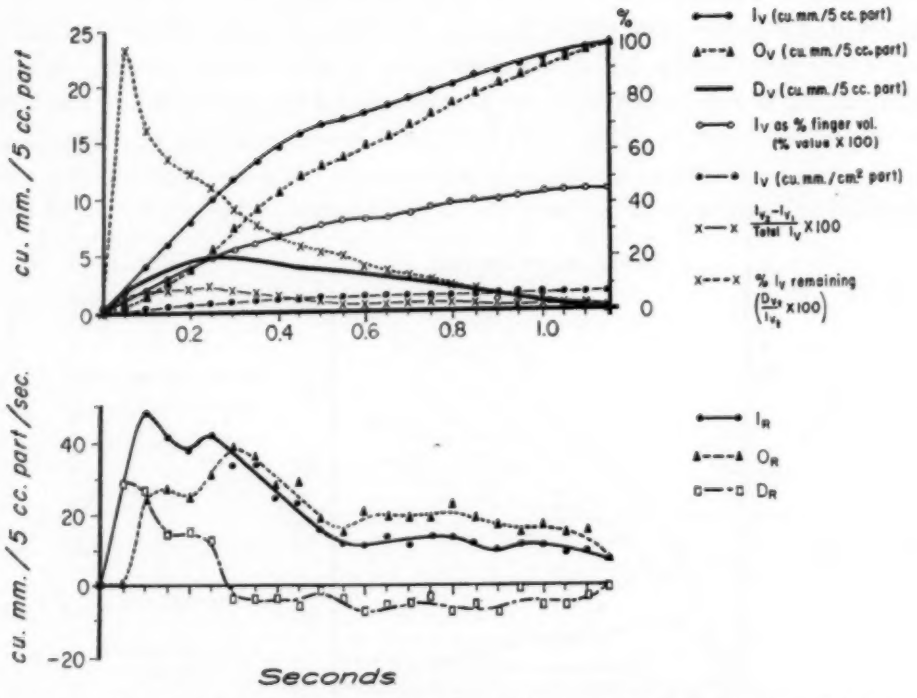

Fig. 7.—Various simultaneous rheoplethysmographic curves of the same subject as Fig. 6 following intravenous administration of 344 mg. noradrenalin (base).

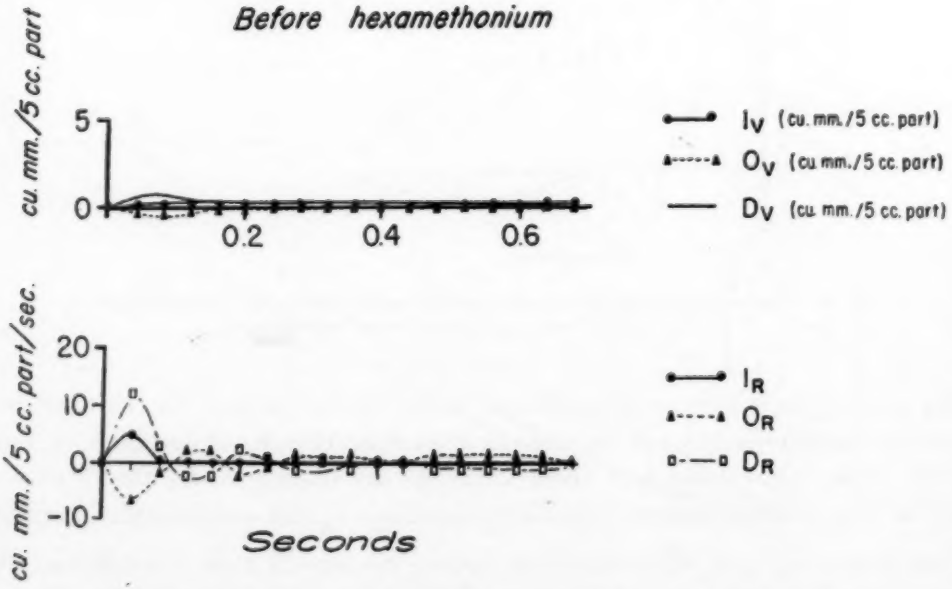

Fig. 8.—Various simultaneous rheoplethysmographic curves of a subject with severe chronic congestive heart failure.

obtained at 0.04- or 0.05-second intervals during the pulse cycle with the use of the expression:

$$\frac{I_{V_2} - I_{V_1}}{\text{Total } I_V} \times 100, \qquad (3)$$

where I_{V_2} is the volume inflow at time t_2, I_{V1} is the volume inflow at time t_1, and total I_V is the total volume inflow during the entire pulse cycle (Figs. 1 to 13).

Comment.—These curves showed remarkable constancy in magnitude of percentile change in I_V despite considerable variations in total inflow and the state of the digital vascular system (Figs. 1 to 13). In only one instance in a normal subject was there a rather significant difference in this percentile curve.

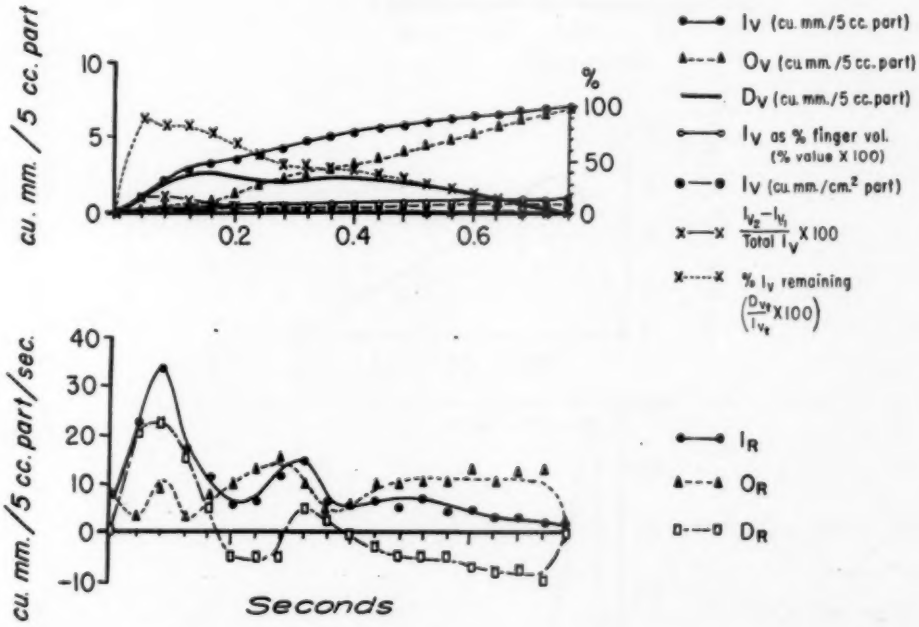

Fig. 9.—Various simultaneous rheoplethysmographic curves of the same subject with congestive failure as Fig. 8 following intravenous administration of 25 mg. of hexamethonium.

The significance of and mechanism for this fairly constant percentile change of the curves throughout the pulse cycle, despite considerable hemodynamic and cardiovascular changes, remain unknown. The percentile change in moment-to-moment inflow was essentially equal to the percentile change in total inflow. The obvious difference between the curve for the subject with aortic valvular insufficiency (Fig. 10) and that for the normal reveals the important influence of a central cardiac lesion upon the pattern of digital flow. This curve also reveals that central cardiac lesions may be reflected in the peripheral circulation.

Time Course of Inflow as Percentage of Total Digital Volume, of Digital Soft Tissue Volume, and of Total Digital Surface Area.—The time courses of accumulated volume of inflow expressed as percentage of total digital volume, of digital soft tissue volume, and of total digital surface area were plotted for single pulse cycles. Selected curves are shown in Figs. 1 to 13.

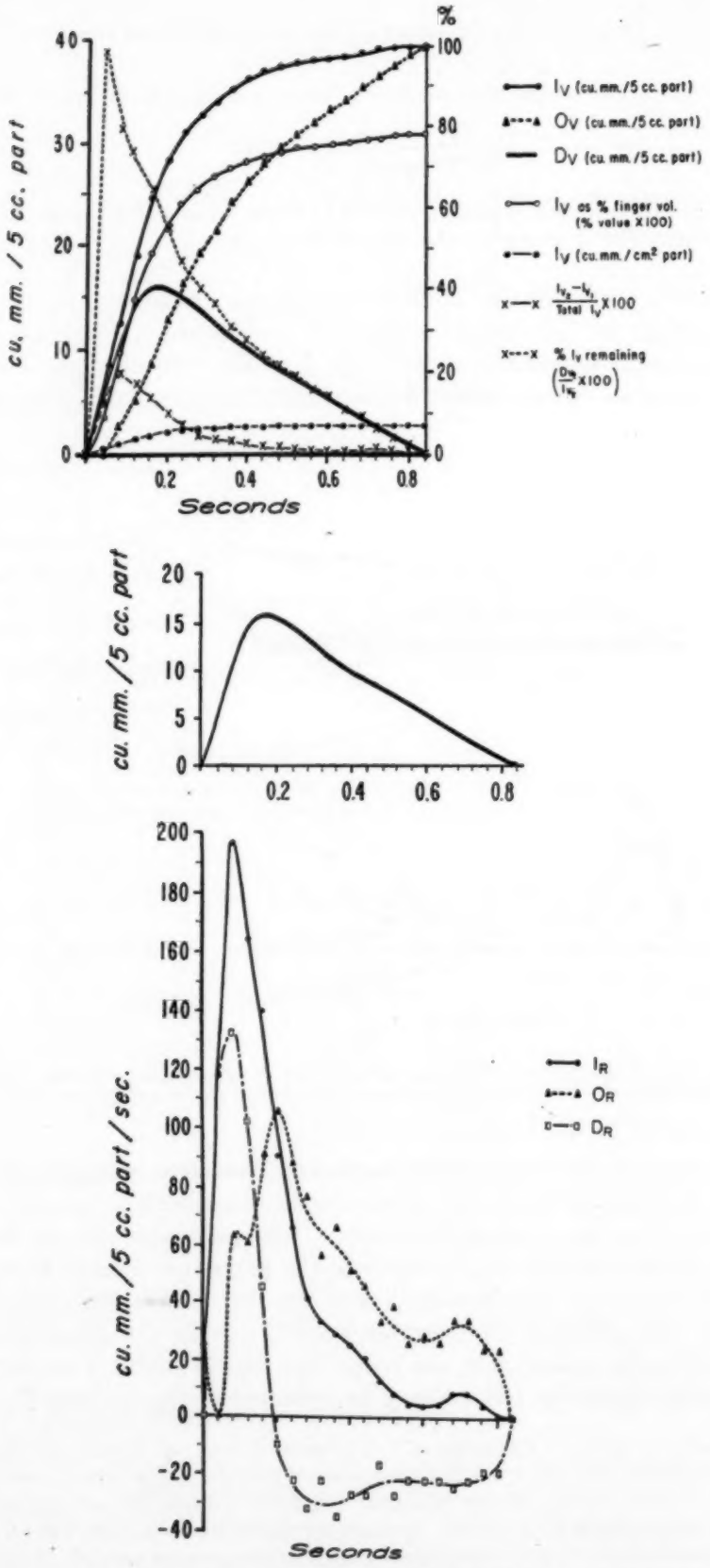

Fig. 10.—Various simultaneous rheoplethysmographic curves of a subject with aortic valvular insufficiency.

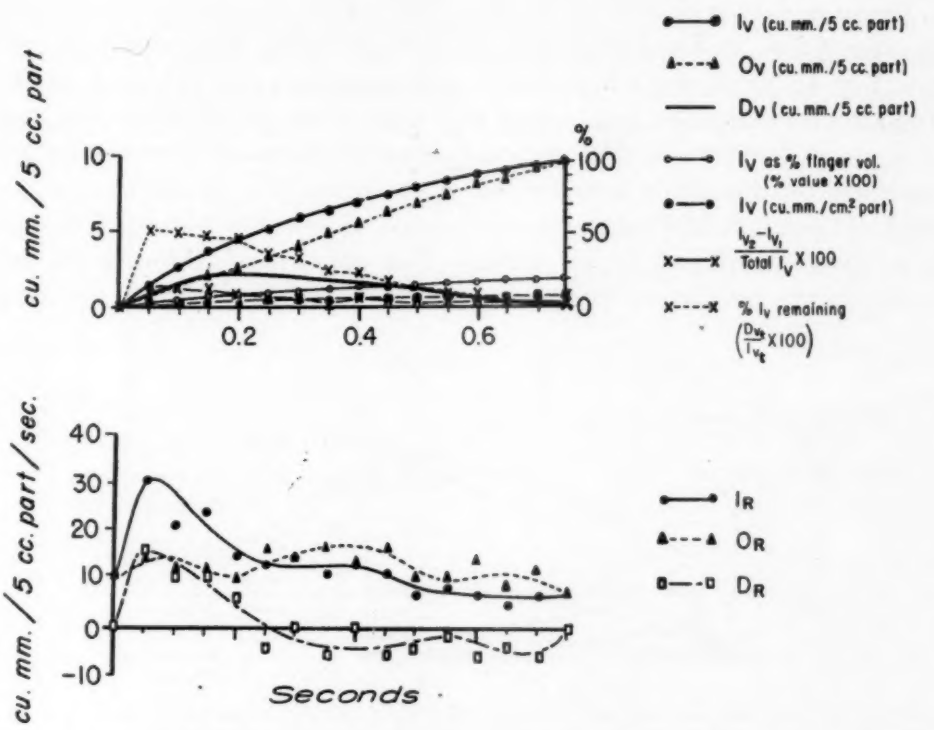

Fig. 11.—Various simultaneous rheoplethysmographic curves of a subject with Raynaud's disease.

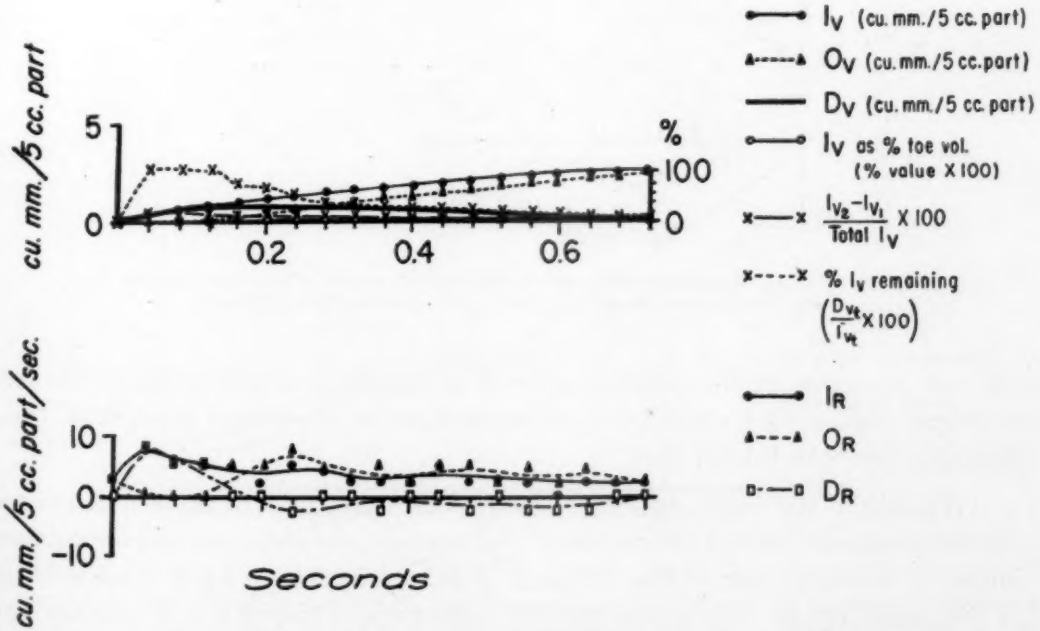

Fig. 12.—Various simultaneous rheoplethysmographic curves of a subject with Leriche's syndrome before aortic bifucation graft.

Comment.—It is evident from these curves that it was only with extremely high rates of flow, such as were found with the subject in a hot and humid environment (Fig. 4), that total inflow during a single pulse cycle exceeded 1 per cent of total digital volume. Total inflow was usually less than 0.8 per cent and was as low as, or lower than, 0.01 per cent when the rates of flow were extremely diminished by disease or pronounced vasoconstriction. Unfortunately, these studies did not indicate the degree or duration of low flow necessary to damage, kill, or cause atrophy of digital tissue. This curve may be found to serve as an index of the circulatory reserve. A cold environment of 15°C. for a lightly

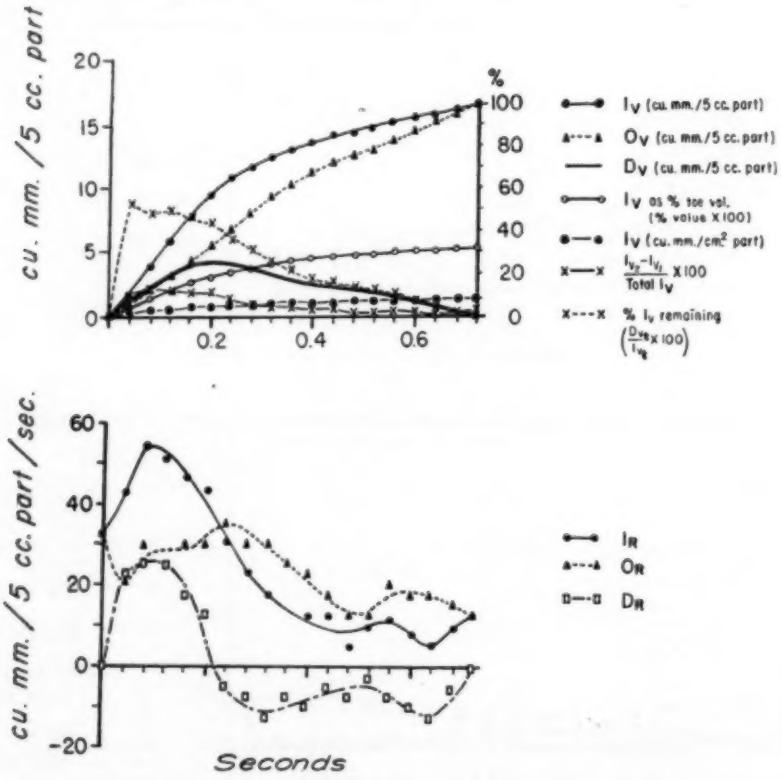

Fig. 13.—Various simultaneous rheoplethysmographic curves of the same subject as Fig. 12 following aortic bifurcation graft for Leriche's syndrome.

clad subject (covered only with a cotton sheet) resulted in volume flows too low to record, even with a rheoplethysmograph sensitive to volume changes of considerably less than 0.1 cu. mm.

A study of the configuration, including the magnitude, of these time course curves reveals interesting information. For example, the time required for volume inflow at the mean rate of flow during a single pulse cycle to equal total volume of the finger tip for an average subject is shown in Table III. In one normal subject (No. 2) resting in a comfortable environment, a volume of blood equal

to the total volume of his finger tip was circulated through his right index finger tip in about one and one-half minutes, and in another (Subject No. 1) a little over two minutes was required for this. With mild vasoconstriction from cold about 22.6 minutes was required in Subject No. 1 for this, over three times longer than in a subject with Raynaud's disease and gangrenous changes in his finger tip (Subject No. 6), in whom only 6.7 minutes was required.

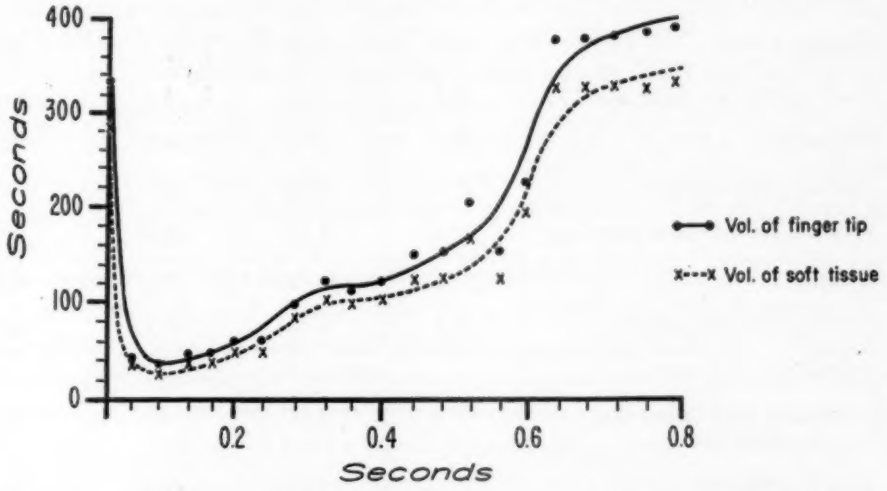

Fig. 14.—Rate of "turnover" of digital blood for a normal subject: the number of seconds at any moment during a pulse cycle that would be required to circulate a volume of blood through the finger tip of a normal adult subject equal to the volume of the total finger tip, and to the volume of the soft tissue, were the rate of inflow for the total finger tip at the respective moments during the pulse cycle to prevail continuously. These curves present in a different manner the time course of the rate of inflow during a single pulse cycle and emphasize strongly the variations in rate and the great magnitude of the maximal rate of inflow attained during the systolic phase of the pulse cycle.

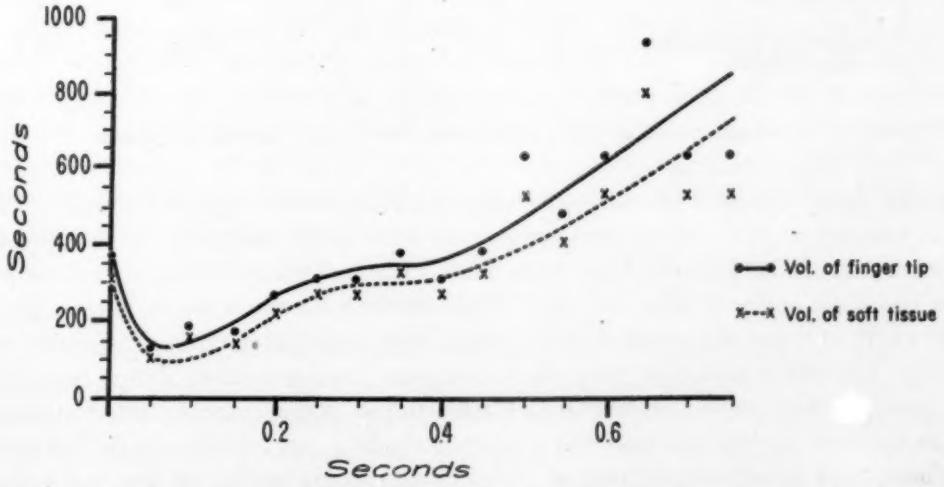

Fig. 15.—Rate of "turnover" of digital blood. Same types of curves as in Fig. 14 but for a subject with Raynaud's disease as illustrated in Fig. 15 for a normal subject. The higher values obtained at the end of the pulse cycle than at the onset are the result of leakage past the occluding cuff and a decline in the A-V pressure gradient following occlusion of venous outflow.[2]

TABLE III. "TURNOVER" OF INFLOW IN DIGIT DURING PULSE CYCLE

SUBJECT NO.	PHYSIOLOGIC AND CLINICAL STATE	VOL. INFLOW PER PULSE CYCLE		MEAN RATE OF INFLOW (CU. MM./5 C.C. PART/SEC.)	TIME OF "TURNOVER" FOR MEAN RATE* (I_V = VOL. FINGER TIP) (SEC.)
		(CU. MM./5 C.C. PART)	(% VOL. DIGIT)		
1	Normal	34.8	0.70	37.8	132.2
	Normal, hand in chamber of cold air	3.1	0.06	3.7	1,355.0
2	Normal	43.2	0.86	54.0	92.6
	Normal, deep inspiration	21.8	0.44	22.7	220.2
	Normal, hot and humid environment	57.3	1.15	68.2	73.4
3	Normal	36.2	0.72	36.2	138.2
	Normal, after norepinephrine	23.2	0.46	20.2	247.8
4	Congestive heart failure		immeasurable	approaches zero	
	Congestive heart failure, after hexamethonium	6.9	0.14	9.1	550.7
5	Aortic insufficiency	39.0	0.78	46.4	107.7
6	Raynaud's disease	9.4	0.19	12.5	399.0
7	Leriche's syndrome	2.6	0.05	3.6	1,384.7
	Leriche's syndrome, after aortic graft	16.4	0.33	22.8	220.0
8	Normal	31.7	0.63	46.6	107.3
9	Aortic insufficiency	28.8	0.58	28.8+	173.6
10	Takayasu's syndrome	29.3	0.59	36.6	136.6
	Takayasu's syndrome, after norepinephrine	8.0	0.16	9.5	525.0

*"Turnover" of digital volume at mean rate of flow. See Table I for digital volume.

The time required for volume inflow to equal total digital volume or soft tissue volume at the rate of flow present at various moments in the pulse cycle is shown for two subjects in Figs. 14 and 15. Careful study of the curves emphasizes the high rates of flow during certain periods of the systolic phase of the pulse cycle and the low rates of flow during the terminal portion of the diastolic phase. The discrepancy in magnitude between the value to t_o, which represents the baseline flow, and the terminal value in the pulse cycle is attributable to errors induced by leakage past the venous occluding cuff, decline in A-V pressure gradient, and other alterations in the hemodynamic state, as the pulse cycle progressed following obstruction to venous outflow. As indicated previously,[1-3] these errors can be reduced considerably by obtaining multiple measurements of flow during successive phases of different pulse cycles. If the errors are remembered during evaluation of the data, this tedious procedure is not necessary, but they certainly must not be ignored.

The rate of blood flow into the finger tip of normal man (46 cu. mm. per 5 c.c. part per second) was evaluated quantitatively by comparison with that for the body as a whole (7.57 cu. mm. per 5 c.c. part per second) and with that for three of the most vital organs, the brain (50.5 cu. mm. per 5 c.c. part per second), kidney (353.3 cu. mm. per 5 c.c. part per second) and liver (88.4 cu. mm. per 5 c.c. part per second) (Fig. 14). It can be seen that the resting rate of digital flow for the subject in a comfortable environment was about equal to cerebral blood flow, was slightly more than one-half of hepatic flow, and about one-eighth of renal flow, but over sixfold the mean flow over all the body tissue. The digital flow varies considerably with environmental and other factors, may increase several fold over average normal flow, with the subject resting comfortably, and may, for short intervals of time at least, decrease to practically zero. Apparently, such wide and frequent fluctuations are not characteristic of the brain, kidney, and liver.

The reasons for the high levels of digital flow are unknown. Sir Thomas Lewis[10] pointed out that digital flow is concerned with local nutrition, local repair, and local, as well as general, thermal regulation. However, these factors fail to explain satisfactorily the high rate of digital flow for normal man at rest under comfortable environmental circumstances. Perhaps the finger tips, for example, need a large supply of blood to maintain proper tactile function. Touch is one of the important senses of man, and the nervous end organs in the digit may require as much blood supply as those elsewhere in the body, including the central nervous system. The paresthesia and numbness of the fingers and toes that follow reduction in blood supply are well known. The volume of blood necessary to maintain good tactile function is unknown and needs investigation. These high rates of digital flow may be made possible by the many arteriovenous shunts found in the digits, such as the complex digital bodies.[11] It would seem that if these A-V anastomoses and high rates of flow were concerned primarily with thermal regulation, they would be concentrated on the palmar surfaces of the digit rather than on the dorsal surfaces, where they could always be exposed to the atmosphere, i.e., where they would not be covered when the hands are closed. If the high rates of digital flow are concerned with nutrition and with a need for large quantities of blood flow to the tactile sensory organs and for repair to trauma from pressure and friction of grasping, they would be concentrated on the palmar surfaces of the digits, where they actually are. This problem has received little or no attention.

GENERAL DISCUSSION

The selected quantitative analyses presented reveal additional approaches to the study of digital flow by means of rheoplethysmography. These continuous curves define not only quantitative aspects of digital flow but also qualitative variations in configuration, permitting another approach to the understanding of peripheral and central circulatory phenomena. Still to be determined is the mechanism by which these curves vary with changes in the normal physiologic hemodynamic state and with cardiovascular disease. Accuracy, reproducibility, and other aspects of recording require detailed study. Differences

in the state of the peripheral or central portions of the circulation are readily reflected in these various curves of the rheoplethysmogram, such as those observed for the resting state, vasoconstriction, aortic valvular insufficiency, and other states discussed in this report (Figs. 1 to 13). There are obviously many other curves that may be obtained from the rheoplethysmograms. No attempt was made to exhaust all of the possibilities.

The high rates of flow to the finger tip may be related to thermal regulation, but other important factors must also be operating. A considerable amount of subtle trauma to the finger tips probably results from friction pressure, knocks, and other forms of mild and severe trauma, at least during use of the fingers and hands, but even that would not seem to explain adequately the high rates of flow for man at rest in bed in a comfortable environment. Large quantities of blood are also required to maintain good health and function for the sensitive tactile Pacinian corpuscles and pain receptors of the finger tips. With exposure to a cool or cold environment, vasoconstriction develops immediately, with associated sharp reduction in digital flow, followed eventually by paresthesia or numbness, a familiar occurrence with cold hands. This vasoconstriction is probably related to conservation of body heat, an extremely significant physiologic phenomenon in maintenance of good general body health, but one that can reduce digital blood supply below local tactile sensory needs to meet the more general body priorities of thermal regulation. With continued exposure to cold, the "hunting phenomenon" of Sir Thomas Lewis develops. Perhaps this reflects an attempt by the circulation to nourish periodically the tactile receptors and warm the tissues periodically, with only periodic exposure of warm blood to the cold and consequent heat loss. This local oscillation in digital blood supply with exposure to cold may be an effort to prevent severe damage and death of the tactile sensory organs and other digital tissues. The reasons for the existence of the hunting phenomenon have never been fully established, and this may be one of them. We have found an occasional person whose hands and fingers seem to be sensitive to the cold and who have lost, or who have a poorly developed, hunting phenomenon.

The rate of "turnover" of blood in the digit or the time required to circulate a volume of blood through the finger tip equal to the volume of the total finger tip is extremely high, varying considerably throughout the pulse cycle, as shown in Figs. 1 to 9. The configuration of the time course of "turnover" varied with the normal and the abnormal cardiovascular states (Figs. 15 and 16). These many quantitative curves permit observation of the digital circulation from several points of view and, thus, more satisfactory study. The time course of inflow remaining as percentage of blood flowing in at any point in the pulse cycle,

$$\frac{I_{V_t} - O_{V_t}}{I_{V_t}} \times 100, \qquad (4)$$

probably reflects in some measure the extent of distention of the digital vascular bed. Although these curves do not actually provide an index of maximal distensibility of the digital vascular system, like the volume pulse wave, they do indicate the time course of actual distention and distensibility of the digital vascular bed.

These studies have shown that when the rate of inflow changes, in general, it does so symmetrically and equally throughout the pulse cycle, even in the presence of extreme vasoconstriction and vasodilatation. Surely, exceptions exist, as noted in some subjects with aortic insufficiency, but even in these the usual biologic variations in the data were observed.

These and other quantitative time course curves are applicable not only to the digits but also to any organ or tissue that lends itself to rheoplethysmography, such as the limbs, kidney, and spleen. Proper adaptation of the rheoplethysmograph to suit the needs of the organ under study is essential, however.

As pointed out previously, as well as in these studies, the rheoplethysmographic method still contains errors due to changes in A-V pressure gradient, limited capacity of the collecting vessels, and leakage past the occluding or collecting cuff. Proper care and effort can reduce these errors to a minimum[1-3] but, unfortunately, involve tedious procedures.

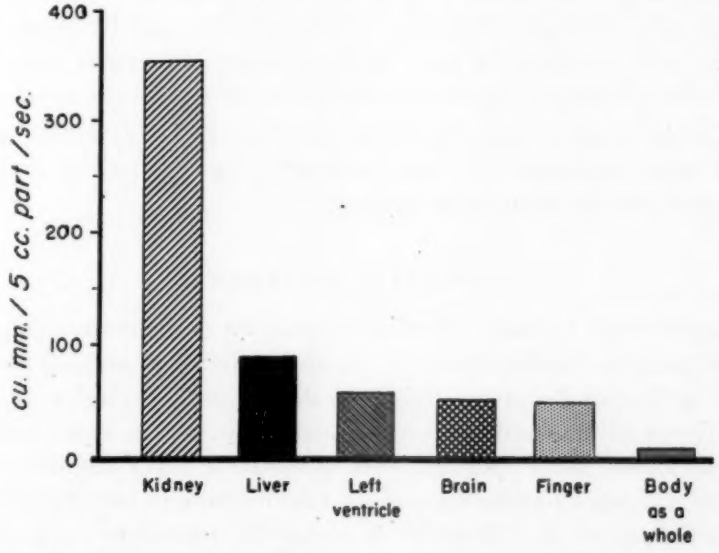

Fig. 16.—Comparison of the resting rates of blood flow in the finger tip of normal man with that in the body as a whole and with that in four vital organs.

SUMMARY

The continuous curves of the time courses of volumes, rates, and accelerations in inflow, outflow, and differences between inflow and outflow in the digits during a single pulse cycle are amenable to various quantitative analyses. These analyses permit a better definition of digital blood flow and provide an additional approach to the study of the physiologic mechanisms responsible for the central and peripheral circulatory states in health and disease. Selected analyses have been presented of more than 300 such digital rheoplethysmograms of ten normal and abnormal subjects; many other analyses are, of course, possible.

Among selected analyses presented are one that simplifies a comparison of the relative proportions of total digital inflow and outflow for any segment of

the pulse cycle, one that demonstrates readily the moment-to-moment lag in outflow with respect to inflow, one that describes temporally the variations in volume inflow as percentage of total inflow, and one that may serve as a possible index of the circulatory reserve. Differences in the state of the peripheral or central portions of the circulation are readily reflected in these various curves of the rheoplethysmogram, such as those observed for the resting state, vasoconstriction, aortic valvular insufficiency, and other states discussed in this report.

In general, the increase or decrease in digital inflow was essentially symmetric and proportional throughout the pulse cycle, even with extreme vasoconstriction or vasodilatation. Particularly significant exceptions were noted in some subjects with aortic valvular insufficiency. The rate of digital flow was observed to be essentially as rapid as that reported for the brain, was over 50 per cent of that reported for the liver, about one-eighth of that reported for the kidney, and several times that reported for the body as a whole. The reasons for these high rates of digital flow are not known but may be related to thermal regulation, as well as other factors, such as those concerned with meeting the needs of the tactile sense so highly developed in the tips of the digits.

Errors in the method may be minimized by careful attention to technique. With proper modifications, the rheoplethysmographic method and its analyses may be adapted for use with other organs.

SUMMARIO IN INTERLINGUA

Es presentate un numero de seligite analyses quantitative de plus que 300 rheoplethysmogrammas digital ab 10 normal e anormal subjectos. Illos rende possibile un meliorate definition del fluxo de sanguine digital e un comprension del mechanismos physiologic que es responsabile pro le stato circulatori e su variationes in statos san e morbide. In general, le total augmento o reduction del influxo digital esseva associate con un essentialmente uniforme e proportional augmento o reduction de influxo in le curso del complete cyclo pulsatil. Exceptiones de signification special esseva notate in certe individuos con insufficientia del valvula aortic. Le prorata del fluxo digital se monstrava essentialmente tanto rapide como illo reportate pro le cerebro; illo esseva plus que 50 pro cento del prorata reportate pro le hepate, circa un octavo de illo reportate pro le renes, e plure vices superior a illo reportate pro le corpore total. Rheoplethysmographia e iste typos de analyse es applicabile a organos altere que le digitos.

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STUDIES ON VASCULAR REACTIVITY IN NORMOTENSIVE AND METACORTICOID HYPERTENSIVE RATS

F. M. STURTEVANT, PH.D.

CHICAGO, ILL.

VASCULAR reactivity, the degree to which the circulatory system responds to vasoactive stimuli, is conveniently assessed by blood pressure reactions to standard drugs.[1] Such responses are of value in investigating possible mechanisms of the production or maintenance of cardiovascular disorders. The present studies were undertaken to examine the vascular reactivity of a relatively new type of experimental hypertension, metacorticoid hypertensive disease in rats.[2] It is reversed by hypophysectomy[3] and nephrectomy,[4] and is alleviated by autonomic-blocking and centrally acting drugs,[2,5] certain steroids[6,7] and diuretics,[8] and starvation.[9]

MATERIALS AND METHODS

The experimental animals consisted of eleven male Sprague-Dawley rats, 306 to 400 grams body weight, and eleven similar rats, 404 to 478 grams, in which metacorticoid hypertension had been induced. This was accomplished by the implantation of a 40 mg. wax pellet containing 20 mg. of desoxycorticosterone acetate (DCA) and the replacement of drinking water by 0.86 per cent sodium chloride solution at least four and one-half months previously.* The non-DCA control rats drank only tap water during this period. At the time of the experiment, the systolic blood pressures of the hypertensive rats ranged from 164 to 188 mm. Hg (mean = 178), as measured without anesthesia or heating using the photoelectric tensometer.[11]

The experiments were performed under urethane anesthesia after heparinization, tracheotomy, and cannulation of the femoral vein and carotid artery. Carotid blood pressure was recorded by kymograph tracings from a small-bore

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From the Division of Biological Research, G. D. Searle & Co., Chicago 80, Ill.

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*Contrary to the assumption of Friedman and associates,[10] the presence of remnants of pellets three months after implantation does not necessarily indicate that the rats are still under the metabolic influence of exogenous DCA. Extracts of DCA-pellet remnants removed from four rats three months after implantation were analyzed photometrically using the blue tetrazolium method by Dr. R. T. Dillon of the Division of Analytical Chemistry. Only 0.2 to 0.3 per cent of the original amount of DCA was still present, and this was heavily encapsulated by a thick fibrous overgrowth.

mercury manometer. The following drugs were injected intravenously, in order, in such concentrations that the desired doses were administered in 1.0 ml. per kilogram:

Epinephrine (Adrenalin chloride, Parke-Davis), 2 mcg. per kilogram;
Norepinephrine (l-Arterenol bitartrate, Winthrop-Stearns), 2 mcg. per kilogram;
Histamine diphosphate (Paul-Lewis), 10 mcg. per kilogram;
Serotonin (5-hydroxytryptamine oxalate*), 60 mcg. per kilogram;
Pitressin (Parke-Davis), 15 mU. per kilogram;
Tetraethylammonium bromide (TEA*), 5 mg. per kilogram;
Yohimbine hydrochloride,* 1 mg. per kilogram.

These were followed by an injection of 0.1 ml. of saline containing 1 mg. of hog renin, purified* according to the method of Haas, Lamfrom, and Goldblatt[12] to a concentration of approximately 1 dog unit per milligram in five steps. With the exception of yohimbine, each injection was repeated at least once immediately after recovery (at least fifteen minutes for Pitressin). After completing the above series of injections, replications were made for a total of two to five series per rat. In addition, some animals received one drug only, throughout a period of several hours. These procedures were of value in uncovering variability of response, change of reactivity with time, and the effect of pretreatment on reactivity.

The significance of differences between group responses was assessed by the rank-sum difference divided by its standard error.[13-15] This approximately normal deviate is similar to the statistic t with infinite degrees of freedom and is significant at the 5 per cent level above ± 1.96 and at the 1 per cent level above ± 2.58. The obvious advantage of this test for significance is that normal distribution and homogeneous variances are not required as in the familiar t-test. The analyses of variance within groups and between groups as a whole were calculated in the usual sum-of-squares manner.

RESULTS

The initial direct blood pressures ranged from 30 to 138 mm. Hg (mean = 86) for the normotensive rats and from 65 to 220 mm. (mean = 146) for the hypertensive rats. This difference was highly significant by the rank-sum test. Data were included from rats in both groups whose pressures were lowered by bleeding.

The over-all course of blood pressure was examined because of the reported downward trends in similar rat preparations.[16] Six normotensive and eight hypertensive rats were studied for a period of four and one-half hours or longer. Half of the normotensives displayed a gradual decline in pressure over this period, while the remainder showed no change or a moderate increase. Three of the eight hypertensive rats also showed this decline, one of them reaching a level 120 mm. below the initial reading five and one-half hours earlier. All rats studied for less than four and one-half hours showed no general tendency for blood pressure decline.

*The author is grateful to Drs. R. Robinson, V. Papesch, W. Voegtli, and R. Snyder of the Division of Chemical Research for the synthesis or purification of these materials.

TABLE I. AVERAGE REACTIVITY OF NORMOTENSIVE (N) AND HYPERTENSIVE (H) RATS TO VASOACTIVE DRUGS

DRUG AND DOSE	GROUP	NO. OF RATS	NO. OF INJECTIONS	BLOOD PRESSURE, MM. HG			
				DECREASE	RANGE	INCREASE*	RANGE
Epinephrine, 2 mcg./Kg.	N	9	31	—	—	26	12–54
	H	11	27	—	—	46†	28–71
Norepinephrine, 2 mcg./Kg.	N	10	37	—	—	33	12–41
	H	11	24	—	—	49‡	29–66
Histamine, 10 mcg./Kg.	N	10	32	17	3–51	25	11–43
	H	10	24	29	3–53	44†	15–65
Serotonin, 60 mcg./Kg.	N	10	32	24	5–62	57	40–89
	H	10	56	27	0–95	113†	40–158
Pitressin, 15 mU./Kg.	N	9	9	9	0–28	26	4–51
	H	10	10	4	0–35	44‡	25–82
TEA, 5 mg./Kg.	N	7	13	—	—	14	3–38
	H	10	21	—	—	22†	6–48
Yohimbine, 1 mg./Kg.	N	9	9	30	18–51	—	—
	H	10	10	56	13–123	—	—
Renin, 2 mg./rat	N	8	8	—	—	57	25–89
	H	10	10	—	—	119†	70–158

*Refers to increase from minima in biphasic responses.
†P <0.01, by rank-sum test.
‡P <0.05, by rank-sum test.

The group responses, represented by the mean pressor and/or depressor values together with their ranges, are given in Table I. In biphasic responses, the secondary phase was measured from the minimum or maximum of the initial phase. Each significance test indicates the probability that the normotensive and the hypertensive responses were drawn from the same population, as determined by the rank-sum method. Table II contains analyses of variance of those log responses which had within-group homogeneous variances: the pressor responses to epinephrine, norepinephrine, histamine, serotonin, Pitressin, TEA, and renin. Seven normotensive and ten hypertensive rats were used for these analyses. This table, which summarizes all of the experiments, indicates significant reactivity within groups and a significantly greater over-all reactivity of the hypertensive group compared to the normotensive group. There was no significant tendency of individual rats to have a greater general reactivity than other rats within the same group.

The responses of both groups to the individual drugs are discussed in the following sections.

Epinephrine and Norepinephrine.—In general, the pressor responses of individual rats were fairly constant in degree, but were varied in type in the case of epinephrine. The hypertensive rats were significantly more reactive to epinephrine and norepinephrine than were the normotensive rats (Table I). The pressor responses were not related to the preinjection blood pressure level.[17]

TABLE II. ANALYSES OF VARIANCE FOR LOGARITHMIC RESPONSES

SOURCE OF VARIATION	DEGREES OF FREEDOM	SUM OF SQUARES	MEAN SQUARE	F	P
Normotensives:					
Rats	6	0.3243	0.0540	1.401	>0.05
Treatments	6	2.1565	0.3594	9.316	<0.01
Error	36	1.3887	0.0386		
Total	48	3.8695			
Hypertensives:					
Rats	9	0.0696	0.0077	0.288	>0.05
Treatments	6	4.2263	0.7044	26.22	<0.01
Error	54	1.4506	0.0269		
Total	69	5.7465			
Comparison:					
N vs. H	1	1.8	1.8	57	<0.01
Pooled error	90	2.8393	0.0315		

Each rat tended to respond to both drugs to a similar degree; however, the response to norepinephrine was somewhat greater than that to epinephrine in the majority of rats (Table I). The question of a progressive change of reactivity of individual rats with time[16] could not be answered definitely, but inspection of the tracings revealed suggestions of such a phenomenon. Yohimbine apparently decreased several subsequent responses to catecholamine injection at varying times afterward, producing epinephrine-reversal in three rats. This cannot be asserted with certainty, however, because in these cases other drugs had been injected after yohimbine and before the catecholamines.

Histamine.—Histamine generally produced an immediate fall in pressure, followed at once by a sharp rise which usually (sixteen in twenty cases) exceeded the preinjection level. The initial depressor response was approximately equal in both groups, while the secondary pressor response was significantly greater in the hypertensive rats (Table I). Moreover, in both groups the depressor phase was significantly more variable than the pressor phase. The nature and degree of the histamine response were not related to the preinjection pressure and were not appreciably altered by pretreatment with multiple injections of Pitressin or serotonin; after one to four series of injections of all drugs, the histamine responses were essentially unchanged in eight hypertensive rats.

Serotonin.—The effect of serotonin in normotensive and hypertensive rats, whether pretreated or not, was of the same general nature: an initial fall in pressure accompanied by bradycardia, followed immediately by a large increase in pressure, and then a slower return to or below preinjection levels. In no case were the responses so variable as those described by Braun-Menendez.[18] The initial depressor phase was equivalent in both groups, while the pressor phase was significantly enhanced in the hypertensives (Table I). The initial fall was significantly more variable than the pressor phase in both groups; neither phase was related to the preinjection pressure level. There was no tendency in either group for tachyphylaxis to the pressor effect of serotonin[19] injected as frequently

as every three minutes. However, there was a decided tendency for the depressor response to become progressively less upon frequent administration: in only two out of sixty-six cases did succeeding injections of serotonin result in a greater initial fall, and in these two cases the increases amounted to only 2 and 7 mm., respectively.

The properties of serotonin have been the subject of two recent reviews by Page [20] and Erspamer.[21] In dogs, serotonin is primarily pressor, while in cats and rabbits it is usually depressor.[19,22-24] The cardiovascular response to serotonin is dependent upon several pharmacologic actions, including a Bezold-like reflex, vasoconstriction, and ganglionic blockade, so that the net effect is mainly pressor when vasoconstrictor tone is low (as after TEA) and mainly depressor when vasoconstrictor tone is high (as after "debuffering").[23] Small doses of serotonin (1 to 5 mcg. per kilogram) produce a depressor effect in rats which can be lessened by autonomic blockade.[25] Although the present data do not confirm the observations of Perry and Schroeder[26] that serotonin was biphasic in normotensive and only pressor in renal hypertensive rats, our data do demonstrate that the pressor component is approximately doubled in metacorticoid hypertensive rats (Table I).

Pitressin.—The majority of rats showed great variability in response to Pitressin. Therefore, for statistical analysis, only the first pressor response of each rat was selected from the total of twenty-two and forty-seven in the normotensive and hypertensive groups, respectively. These initial pressor responses were significantly greater in the latter group (Table I). In three normotensives and four hypertensives, the rise in blood pressure was preceded by a variable fall of short duration (Table I). The responses did not appear to be related to the preinjection pressure level nor to pretreatment other than with Pitressin itself, in which case tachyphylaxis usually persisted up to twenty to thirty minutes after injection. We previously reported that large (25 units per kilogram) subcutaneous doses of Pitressin lowered the blood pressure of unanesthetized metacorticoid rats.[8]

TEA.—The responses to repetitive injections of TEA in individual animals of both groups were fairly regular, usually monophasic and pressor, and independent of preinjection pressure level and pretreatment. However, five of the hypertensive rats displayed a secondary depressor response of 38 to 76 mm. (mean = 52). This does not agree with the comment of Braun-Menendez that "repeated injections of TEAC in hypertensive or normal rats always give depression of blood pressure."[18] For statistical comparison, only the first group of TEA responses in each rat was used. The hypertensives again were significantly more sensitive to the pressor action of TEA (Table I).

The hypotensive action of TEA is attributable to the production of ganglionic blockade,[27,28] the hypertensive action to hepatic and adrenal secretion of pressor amines.[28,29] Repetitive injections of TEA in other species cause a reversal from a depressor to a pressor type[30,31] and result in the potentiation of pressor drugs, presumably due to ganglionic blockade of homeostatic reflexes.[32-37] Although the latter phenomenon was not under investigation, inspection of the

tracings yielded no suggestion of potentiation in the doses employed. One normotensive rat received thirteen successive injections of TEA, 5 mg. per kilogram, during a four-hour period. Responses varied from biphasic to monophasic, without progression toward either type or intensification of either component. Epinephrine and norepinephrine responses following this pretreatment were not any greater than the group average.

Yohimbine.—The response to yohimbine was always an immediate, sharp, and prolonged fall of blood pressure. By inspection, these falls appeared to depend upon the preinjection pressure level in both groups. Based on an analysis of variance of the regressions of (log X − log Y) on log X, where X is the preinjection pressure and Y is the minimum after injection, the hypotensive responses of the normotensive rats were directly and arithmetically proportional to the preinjection level, while the responses of the hypertensive rats were proportional to the square root of the preinjection level. Therefore, either (1) there was a qualitative difference in response between the two groups, in that the hypertensives had a progressively increasing sensitivity to yohimbine the higher the blood pressure; or (2) the true relationship between response and initial pressure was of a nonallometric type. The former suggestion is reminiscent of the purportedly increased sensitivity of renal hypertensive rats to adrenergic blockade.[38-41]

There was no evidence of serotonin-reversal[42] in nine rats that received a second series of serotonin injections after yohimbine, although such a phenomenon could have been missed because of the time interval between the two injections.

Renin.—The response to renin was invariably a typical, sharp, prolonged increase in pressure. It was unrelated to the preinjection level, as described previously.[17,43,44] The reactivity of the hypertensive rats was approximately doubled (Table I); this could not be ascribed to differences in age.[45] The type of renin employed was found to induce tachyphylaxis in both groups of rats.

DISCUSSION

We have concluded from the literature* that renal hypertensive rats may display an increased vascular reactivity to epinephrine, adrenergic blocking drugs, serotonin, and renin; on the other hand, desoxycorticosterone acetate (DCA) hypertensive rats do not display marked increase in reactivity to epinephrine or Pitressin, while the question of renin sensitivity is unsettled. In the present experiment, metacorticoid hypertensive rats exhibited a fairly general increase in reactivity to the pressor effects of the two catecholamines, histamine, serotonin, Pitressin, TEA, and renin, but not to the depressor effects of histamine, serotonin, or TEA. No comparison could be made in the case of yohimbine, because the responses to it varied with the initial pressure in a different manner in the two groups. The lack of dependence of the other drug responses on the initial pressure confirms previous observations of Page.[33,43]

*Review of the literature available on request.

The degree of variability experienced in these studies was much less than had been expected on the basis of the excellent studies on dogs reported by Page and co-workers.[22,23,28,30,32,33,42-44,46] It is conceivable, however, that more exhaustive studies on larger numbers of rats may yield more precise information on the variability in such vascular reactivity experiments, and so alter the quantitative differences derived from the present set of data.

In conclusion, evidence has been presented for a heightened sensitivity of the circulatory system of metacorticoid hypertensive rats to certain direct and indirect pressor stimuli. This increased reactivity may well represent an important effector mechanism that obtains in rats no longer under the acute action of DCA and the abnormalities of electrolyte exchange induced by it. How the period of DCA-sodium treatment brings about this hyperreactivity remains to be elucidated.

SUMMARY

The vascular reactivity of normotensive and metacorticoid hypertensive rats was assessed by direct blood pressure responses to intravenous injections of epinephrine, norepinephrine, histamine, serotonin, Pitressin, tetraethylammonium, yohimbine, and renin. The hypertensive rats were significantly more sensitive than the normotensive rats to the pressor effects of all drugs except yohimbine. The latter was depressor to a degree dependent upon the basal blood pressure, and no difference in response could be demonstrated.

SUMMARIO IN INTERLINGUA

Le reactivitate vascular de rattos con normotension e con hypertension inducite per metacorticoide esseva evalutate per medio del responsa directe del pression sanguinee a injectiones intravenose de epinephrina, norepinephrina, histamina, serotonina, Pitressina, tetraethylammonium, yohimbina, e renina. Le rattos hypertensive esseva significativemente plus sensibile que le rattos normotensive al effectos pressori de omne iste drogas excepte yohimbina. Isto esseva depressori a un grado dependente del basal pression sanguinee, e nulle differentia in responsa in le duo gruppos esseva demonstrabile.

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CHANGES IN CARDIAC RHYTHM AND IN THE FORM OF THE ELECTROCARDIOGRAM RESULTING FROM INDUCED HYPOTHERMIA IN MAN

R. W. Gunton, M.D.,* J. W. Scott, M.D., W. M. Lougheed, M.D., and E. H. Botterell, M.D.**

Toronto, Ontario

THE use of hypothermia in cardiac surgery was suggested by Bigelow and associates[1] and has subsequently been employed by a number of cardiac surgeons.[2-4] With lowering of body temperature the total oxygen requirement of the body is reduced,[5-7] allowing interruption of blood flow through the heart for periods of time sufficiently long to perform certain intracardiac procedures under direct vision.

The employment of hypothermia in neurosurgery was described by Lougheed, Sweet, White, and Brewster[8] and has been more extensively used by Botterell, Lougheed, Scott, and Vandewater.[9] When the body temperature is reduced to 28° C., bilateral occlusion of the carotid and vertebral arteries is tolerated for ten minutes, permitting surgical treatment of recently ruptured intracranial aneurysms or arteriovenous malformations.

A recognized risk of hypothermia is the occurrence of vertricular fibrillation and cardiac arrest, particularly at temperatures below 28°C.[11] The electrocardiographic changes in hypothermic animals have been fully reported,[1,6,12,13] and similar observations have been made on human subjects with heart disease at the time of operation under hypothermia.[14]

There have been few reports of the effect of hypothermia on the rhythm and form of the electrocardiogram of human subjects without heart disease. This information may be of theoretical and practical importance with the wider use of hypothermia in cerebrovascular surgery or other specialized types of surgery where thoracotomy is not performed.

The authors have had the opportunity to record and study electrocardiograms from twenty-nine adult patients in whom hypothermia was induced for neurosurgical procedures.

MATERIAL AND METHODS

In the total of twenty-nine cases there were twenty-three ruptured congenital "berry" aneurysms, three congenital arteriovenous malformations, two brain tumors, and one congenital hemiplegia with epilepsy. Three of the patients

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*Senior Medical Research Fellow, National Research Council, Canada.

**From the Departments of Medicine and Surgery, University of Toronto, and the Neuro-surgical Service, Toronto General Hospital.

had known heart disease: of these two had hypertensive heart disease and one had rheumatic heart disease with mitral stenosis. Two additional patients had T-wave abnormalities in the preoperative electrocardiogram, but did not have clinically recognized heart disease.

The technique of anesthesia and hypothermia has been described elsewhere.[15] Preoperative medication consisted of promethazine 50 mg., chlorpromazine, 50 mg., and pethidine 50 mg., all given intramuscularly. Ten patients received thiopentone intravenously prior to intubation of the trachea. The lower limbs and trunk were immersed in ice water. Reduction of the body temperature to 28°C. to 30°C. usually required about one and one-half hours, and it was then maintained at this level for an additional two to four hours. In five patients systemic hypotension was induced during the intracranial surgery using hexamethonium bromide in one case and trimethan camphorsulfonate (Arfonad) in four cases.

Electrocardiograms were taken several days before operation on nineteen patients. In the operating room, after the early anesthetic procedures and before lowering the body temperature, an electrocardiogram was recorded on all patients. It was usually possible to obtain the standard and unipolar limb leads and at least one precordial lead. Throughout the operation one lead was observed continuously on a cathode ray oscilloscope and recorded continuously on one channel of an electroencephalograph. At various body temperatures, and at times when a change in the rhythm was noted, as many leads as possible were recorded. Further records were made one to twelve days after operation.

The heart rate, length of P-R and Q-T intervals, the duration of QRS complexes, and changes in S-T segments and T waves were recorded. The measurements from the electrocardiogram taken at the lowest body temperature were compared with those from the record taken at normal body temperature. These comparisons were made only in those cases where sinus rhythm persisted well into hypothermic levels (29 to 31°C.). Auricular fibrillation appeared in many of the patients, producing an alteration in the heart rate and distortion of QRS complexes and T waves. These changes precluded precise measurement and could not properly be ascribed to hypothermia alone.

The heart rate was altered not only by the arrhythmias but probably also by operative movement of intracranial structures, carotid manipulation, and blood loss. Ten cases, however, were considered suitable for comparison of the heart rate in the normothermic and the hypothermic states.

RESULTS

Heart Rate.—(Ten comparisons). In eight cases there was a decrease in the heart rate. The mean decrease was 23 per minute from an average rate of 94, during dissection of the neck vessels and prior to hypothermia, to a mean rate of 71 at the lowest body temperature. In the patient with the greatest fall in heart rate, a sinus bradycardia of 41 per minute appeared to be associated with traction on the carotid arteries; administration of atropine increased the rate to 75 per minute. In one patient there was no change in rate and in one the rate rose from 94 to 130 per minute.

P-R Interval.—(Thirteen comparisons). In seven cases there was a measurable increase of the P-R interval and in the remaining six there was no change. The range of increase was 0.02 to 0.05 second. Complete heart block did not occur in any case.

QRS Complex.—(Thirteen comparisons). In seven cases there was a lengthening of the QRS complex by 0.01 to 0.04 second. In the remaining six cases no measurable change occurred.

Q-T Interval.—(Thirteen comparisons). Duration of electrical systole was calculated using Bazett's formula: $K = \frac{Q-T}{\sqrt{R-R}}$. There was a lengthening

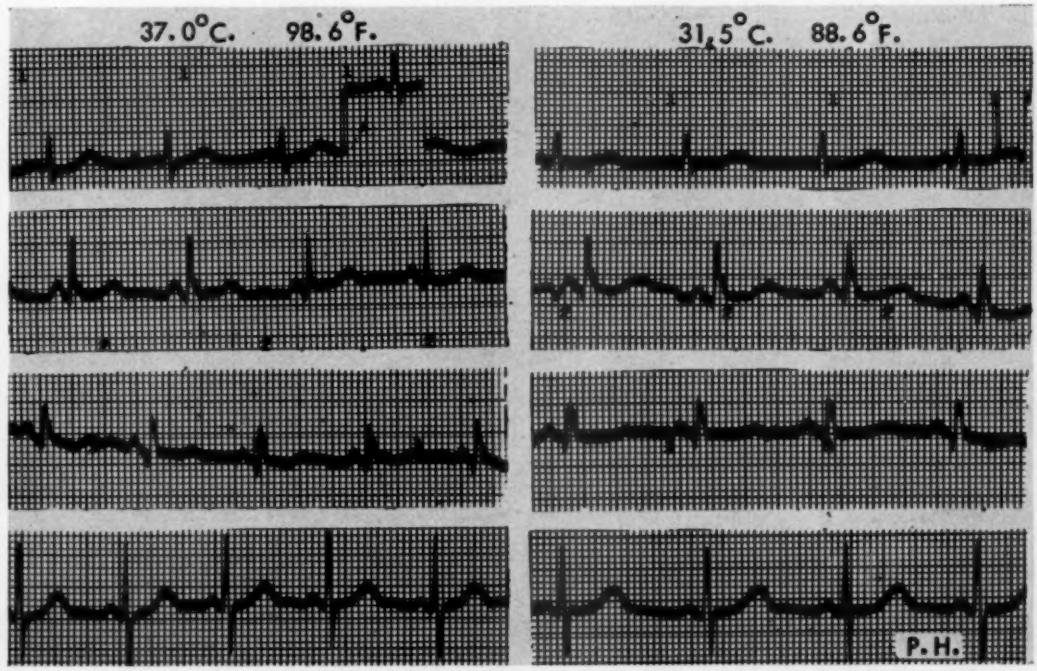

Fig. 1.—Patient, P.H., woman, aged 32 years. Electrocardiograms at normal body temperature (37°C.) and during hypothermia (31.5°C.) showing decrease in heart rate and prolongation of P-R and Q-T intervals and QRS complex.

of electrical systole in nine cases, ranging from 0.01 to 0.17 second. The mean K value in all thirteen cases was 0.445 second at normal temperature and 0.474 second at the lowest temperature.

T Wave and S-T Segment.—(Thirteen cases). In all thirteen cases where comparisons could be made uninfluenced by arrhythmias, definite lowering, flattening, or inversion of T waves in one or more leads was observed in eight cases and depression of the S-T segment by 1 millivolt or more in five cases.

Rhythm.—(Twenty-nine cases.) Sinus rhythm was maintained throughout the period of hypothermia in only nine cases. One patient who had rheumatic heart disease with auricular fibrillation preoperatively continued to have auricular

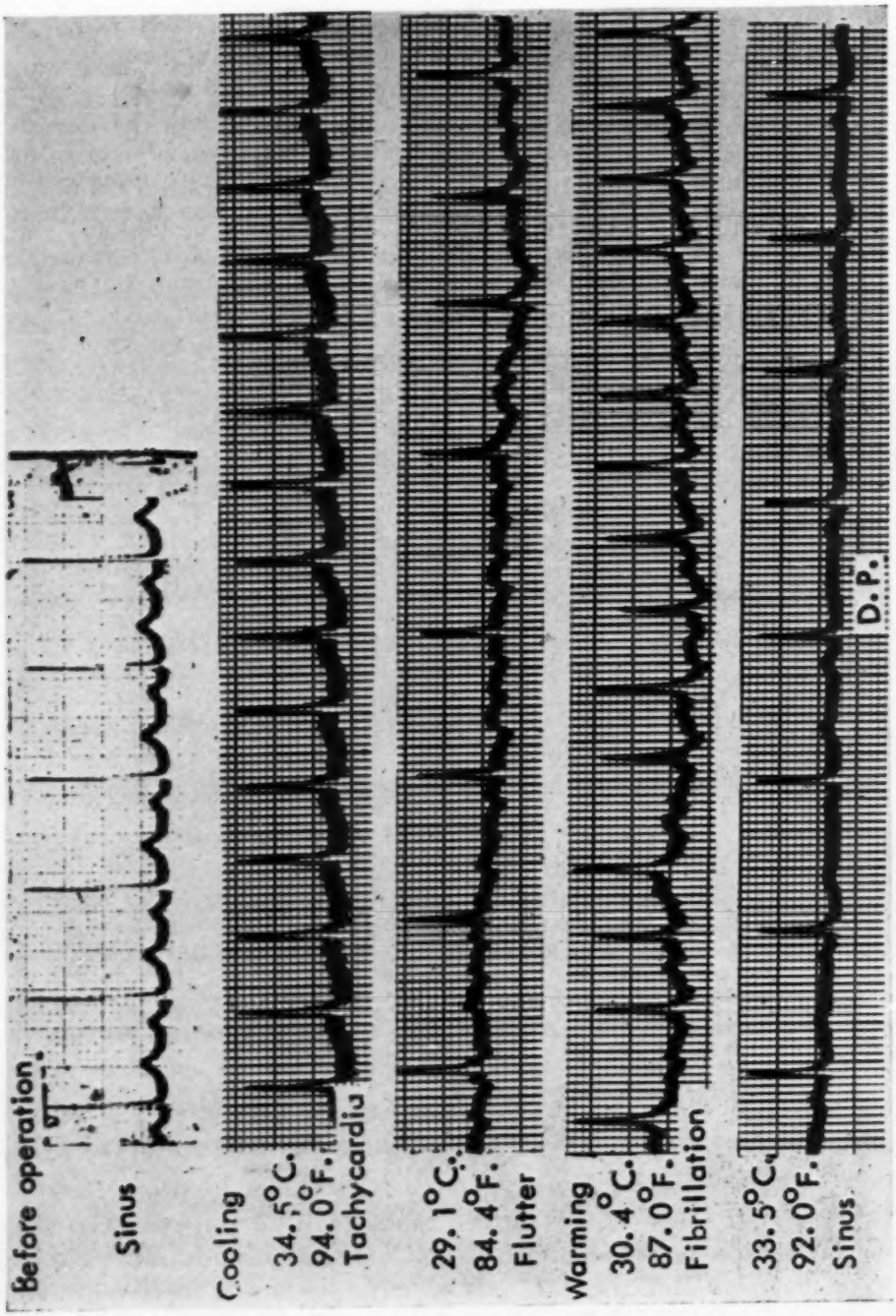

Fig. 2.—Patient, D.P., woman, aged 33 years. Lead II of the electrocardiogram recorded during hypothermia, showing change from sinus rhythm preoperatively to a regular supraventricular tachycardia, auricular flutter, and then auricular fibrillation during hypothermia. Reversion to sinus rhythm occurred in the rewarming period.

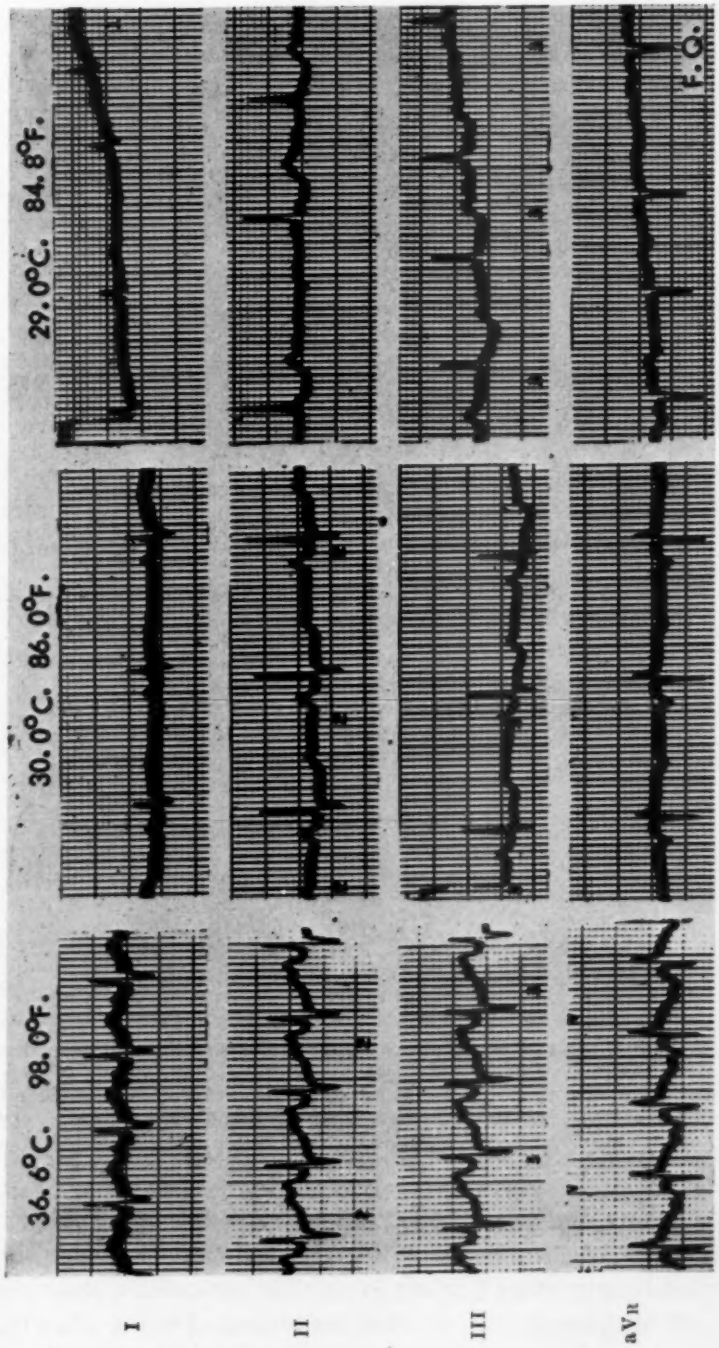

Fig. 3.—Patient, F.Q., woman, aged 36 years. Electrocardiograms recorded at body temperatures of 36.6°C., 30.0°C., and 29.0°C. In the record at 30.0°C. sinus rhythm has been maintained but changes in the S-T segments and T waves have appeared. At 29.0°C. there is auricular fibrillation associated with further S-T and T changes.

fibrillation during hypothermia. In the remaining nineteen cases the following abnormalities were observed:

Auricular arrhythmias:

Wandering pacemaker	2
Auricular tachycardia	1
Auricular flutter alone	1
Auricular flutter and auricular fibrillation	1
Auricular fibrillation alone	12

Ventricular fibrillation: (Both preceded by auricular fibrillation) 2

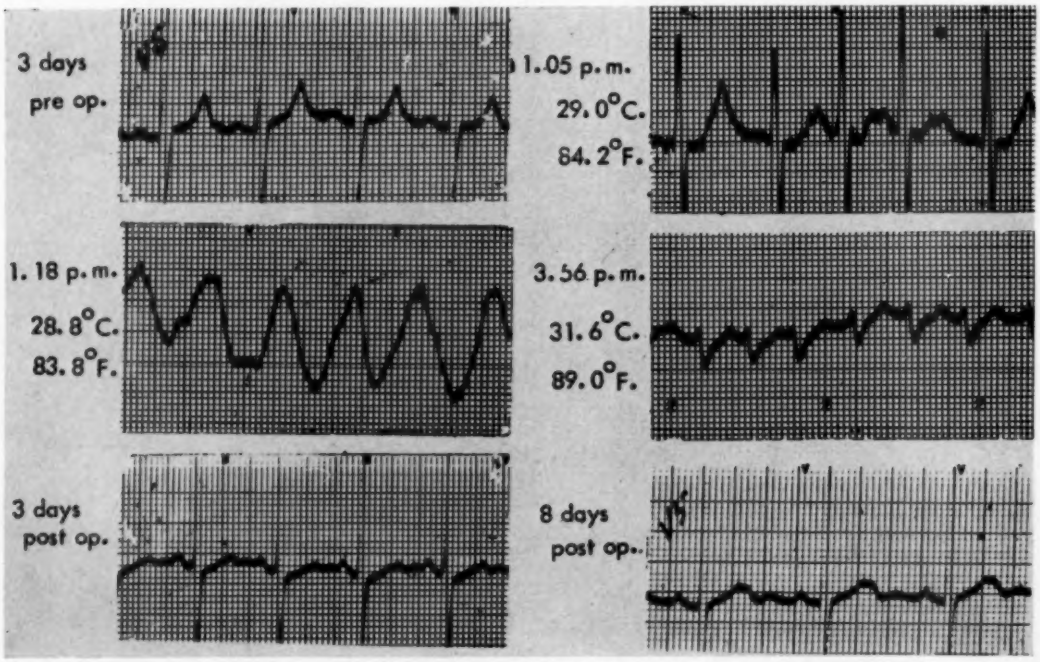

Fig. 4.—Patient, E.C., man, aged 50 years. Serial electrocardiograms show the presence of auricular fibrillation at a body temperature of 29.0°C., followed by ventricular fibrillation at 28.8°C. Spontaneous irregular ventricular contractions (basic rhythm probably auricular fibrillation) returned following cardiac massage and rewarming. In the records taken three and eight days after operation the rhythm was sinus but deformity of the T waves persisted.

Auricular fibrillation and the other auricular arrhythmias usually appeared at body temperature between 30 and 28°C. In one case auricular fibrillation was clearly preceded by auricular flutter; in some other cases a clear distinction between flutter and fibrillation was difficult to make. During auricular fibrillation the ventricular rate was not excessive, seldom rising above 120 per minute. There was usually a fall in systemic blood pressure during the period of hypothermia and surgery, but the appearance of an auricular arrhythmia did not produce a further noticeable fall.

Once established, the arrhythmia usually continued throughout the period of hypothermia. In a few patients reversion to sinus rhythm was observed in the operating room during the rewarming period. In the electrocardiograms taken one to four days after the operation a normal sinus rhythm was always found. Exact information concerning the time of reversion to a sinus rhythm was not obtained because electrocardiograms were not recorded in the early postoperative period. By clinical examination the rhythm was usually regular six hours after operation and always on the first postoperative day. It was assumed that restoration of a sinus rhythm usually occurred at the time body temperature approached normal levels four to six hours after termination of the operation.

In a 54-year-old man without known heart disease and with a normal preoperative electrocardiogram, auricular fibrillation appeared at a body temperature of 32°C. and ventricular fibrillation at 28°C. When the ventricular rhythm had persisted for fourteen minutes the chest was opened and cardiac massage commenced. Spontaneous cardiac contractions returned after fifty-five minutes and the electrocardiogram showed auricular fibrillation with rapid irregular ventricular responses. The patient survived and was completely well. Three days after operation the electrocardiogram revealed a sinus rhythm with low T waves in Leads V_5 and V_3. Eight days after operation the record was within normal limits but differed slightly from the preoperative record (Fig. 4).

In a woman aged 58 years with known hypertensive heart disease, auricular fibrillation appeared at 32°C. and ventricular fibrillation at 28.7°C. Cardiac massage was performed but was unsuccessful in restoring spontaneous cardiac contractions.

In these two patients who developed ventricular fibrillation, systemic hypotension had been induced during the operative procedure.

Isolated ventricular premature beats occurred in many patients during hypothermia, but in only one case did they appear in runs suggesting the danger of ventricular tachycardia.

POSTOPERATIVE PERIOD

Restoration of sinus rhythm in the postoperative period has already been mentioned.

Minor changes in the T waves and the S-T segments were present in electrocardiograms taken one to four days after operation in eight cases. In four of these the changes appeared to have persisted from the hypothermic period. In the other four cases the abnormalities were not present in the tracings taken during the surgical procedure. Whether these late changes should be attributed to direct or indirect effects of hypothermia is a doubtful point. The occurrence of sinus tachycardia due to fever, or anoxia due to airway obstruction in the early postoperative period may have separately influenced the electrocardiogram.

In the group of twenty-nine patients reported in this study there were four deaths. One was directly attributable to hypothermia. This was the case of ventricular fibrillation to which reference has already been made. The other three patients died of noncardiac causes, one each of: massive intracerebral clot and cerebral infarction encountered at operation; postoperative cerebral compression; late terminal inanition and bronchopneumonia.

DISCUSSION

The effect of hypothermia in depressing the electrical activity of the heart of experimental animals has been well documented.[1,6,12,13] Slowing of heart rate, prolongation of P-R, QRS, and Q-T intervals and changes in the S-T segments and the T waves have been repeatedly observed. The frequent occurrence of ventricular fibrillation or ventricular standstill in laboratory animals, particularly dogs, cooled to 24°C. or lower has been emphasized by several authors.[1,16,17] Few references to auricular arrhythmias occurring in hypothermic animals have been made. Bigelow and associates[1] have reported from direct observation that after the onset of ventricular fibrillation in the hypothermic dog, the auricles continue to beat regularly for a while.

The observations made in the present study, together with the reported experiences of others using hypothermia in human subjects, suggests that auricular arrhythmias are common at body temperatures in the range of 28° to 30°C. In 1940, during investigations on the effect of lowering body temperature on the growth of malignant tumors, Kossmann[18] reported electrocardiographic changes in nine subjects whose body temperatures had been reduced to 85°F. for many hours. He observed prolongation of QRS and Q-T segments, T-wave changes, and the appearance of auricular fibrillation in four of the nine subjects. Talbott,[19] in his review of the therapeutic effects of hypothermia, reported the occurrence of auricular fibrillation in all twenty patients subjected to hypothermia. Exposure to cold following shipwreck or other misadventure has been reported to cause transitory auricular fibrillation in humans without known heart disease.[20,21] The observations of Hicks and associates[14] in patients with heart disease in whom hypothermia was induced for direct-vision surgery of the open heart are similar to those reported in the present study. Auricular fibrillation occurred in ten of their twenty-two patients.

Hypothermic auricular fibrillation in human subjects appears to be a common benign arrhythmia which is limited to the period of lowered body temperature and does not produce important hemodynamic disturbances.

Ventricular fibrillation is the principle hazard in hypothermia, particularly at body temperatures below 24°C.[11] It occurred in two patients in the present series at 28°C. Although the ventricular fibrillation in each case was preceded by auricular fibrillation, it cannot be concluded that the auricular arrhythmia warned of the imminence of ventricular fibrillation. It is reasonable to speculate that the mechanism may be the same; the ventricle, in man, retaining the capacity for normal contraction at lower temperatures than the auricle. This does not appear to be true in dogs.

The factors responsible for ventricular fibrillation and cardiac arrest in hypothermia have been diligently sought by many investigators. Depression of the rate of impulse production in the S-A node and slowing of the rate of impulse conduction as evidenced by prolongation of P-R interval and QRS complex, have been commonly observed effects of cold. Extreme depression of the cardiac pacemakers and conducting tissue might explain slow idioventricular rhythms or ventricular standstill. The sudden development of ventricular fibrillation suggests an altered state of the heart muscle in addition to depression of the specialized stimulating and conducting tissues.

Evidence that anoxia of the myocardium does not exist in hypothermia has been presented by Penrod and Flynn[22] in the observation that the coronary arteriovenous oxygen difference is normal in dogs cooled to 20°C. Hegnauer and D'Amato[7] concluded that there was no general tissue anoxia in dogs cooled to 17°C. and observed that an oxygen debt could be corrected by the hypothermic animal.

Swan and associates[4] and Fleming[23] have reported that respiratory acidosis increases the incidence of ventricular fibrillation in hypothermic dogs. Positive pressure artificial respiration with pure oxygen to elevate blood pH has been recommended in the clinical application of hypothermia.[11] However, in their series of human subjects cooled for cardiac surgery, Hicks and associates[14] found no relation between blood pH and disturbances in cardiac rhythm.

Current interest in the role of potassium in cardiac arrhythmias has directed attention to myocardial potassium transfer in hypothermia. Swan and associates[4] have reported that intra-arterial injection of potassium may correct ventricular fibrillation in the hypothermic dog. Montgomery, Prevedel, and Swan[24] later observed that the hypothermic myocardium in ventricular fibrillation loses potassium. They found that prostigmine, acetylcholine, and vagal stimulation have an antifibrillatory effect upon the ventricular myocardium of the hypothermic dog and believe this effect is due to potentiation of flow of potassium across the cell membrane.

Positive pressure artificial respiration was not used in the present series of cases, so that its efficacy in preventing cardiac arrhythmias cannot be judged.

Auricular fibrillation occurred in the three patients with known heart disease (it was present preoperatively in one) and in the two additional patients with abnormal preoperative electrocardiograms. Fatal ventricular fibrillation occurred in one patient. The patients who maintained sinus rhythm throughout the period of hypothermia tended to be in a younger age group than those who developed auricular fibrillation. These considerations have prompted caution to the extent that body temperatures below 30°C. have been avoided by the surgical and anesthetic staff in older patients or in those with heart disease.

SUMMARY

Electrocardiograms were recorded in twenty-nine adult patients during hypothermia which was induced for the performance of cerebrovascular surgery. Twenty-four of the patients had no clinical or electrocardiographic evidence of heart disease.

At body temperatures of 28 to 30°C. electrocardiographic abnormalities appeared in many of the patients. The heart rate slowed; the P-R and Q-T intervals and the duration of the QRS complex were lengthened; S-T segment and T-wave changes appeared. Auricular fibrillation or other auricular arrhythmias occurred in nineteen patients.

Ventricular fibrillation occurred in two patients. Cardiac massage was followed by recovery in one of these.

The change in impulse origin and conduction and the auricular arrhythmias did not produce serious hemodynamic disturbances. Postoperatively at normal

body temperature, the electrocardiograms revealed a return to sinus rhythm. In a few cases the S-T segment and T-wave changes persisted or appeared in the first few days after operation.

It is concluded that auricular fibrillation is a frequent occurrence when the body temperature of human subjects without heart disease is lowered to 28 to 30°C. Usually this arrhythmia is benign, restricted in time to the period of hypothermia, and is not followed by a disturbance of heart function.

SUMMARIO IN INTERLINGUA

Le electrocardiogrammas de 29 patientes adulte esseva registrate durante hypothermia que esseva inducite pro le execution de chirurgia cerebrovascular. Vinti-quatro del patientes habeva nulle indicios clinic o electrocardiographic de morbo cardiac.

A temperaturas corporee de inter 28 e 30 C, anormalitates electrocardiographic appareva in multes de iste patientes. Le frequentia cardiac deveniva plus lente; le intervallos P-R e Q-T e le duration del complexo QRS esseva allargate; cambiamentos appareva in le segmento S-T e le unda T. Fibrillation auricular o altere arrhythmias auricular occurreva in dece-octo casos.

Fibrillation ventricular occurreva in duo patientes. In un de iste casos massage cardiac esseva sequite per restablimento.

Le cambiamentos in le origine e le conduction de impulsos, e le arrhythmias auricular, non produceva grave disordines hemodynamic. Le electrocardiogrammas postoperative, prendite a normal temperaturas corporee, revelava un retorno a rhythmo sinusal. In alicun casos le cambiamentos del segmento S-T e del unda T persisteva o reappareva durante le prime dies post le operation.

Nos conclude que fibrillation auricular es un occurrentia frequente in humanos sin morbo cardiac quando lor temperatura corporee es reducite a 28 o 30 C. Generalmente iste arrhythmia es benigne, es restringite in tempore al periodo de hypothermia, e non es sequite per ulle disrangiamento del function cardiac.

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THE CLINICAL AND HEMODYNAMIC PATTERN IN NONSPECIFIC MYOCARDITIS: A COMPARISON WITH OTHER ENTITIES ALSO IMPAIRING MYOCARDIAL EFFICIENCY

OSCAR J. BALCHUM, M.D., PH.D.,* MALCOLM C. MCCORD, M.D.,† AND S. GILBERT BLOUNT, JR., M.D.

DENVER, COLO.

MYOCARDITIS is a commonly occurring lesion which may be associated with a wide variety of known disease entities. However, no apparent associated disease or etiologic factor can be identified in a significant number of patients with myocarditis.[1,2] The term nonspecific myocarditis has been applied to this latter group. This disease process has received increasing reference in the literature as the basis of a syndrome characterized by cardiomegally, congestive failure which is largely refractory to therapy, and the absence of evidence of a specific etiology.[3] The clinical features of patients with this entity may be similar to those accompanying disease processes amenable to specific therapy, such as pericardial effusion and constrictive pericarditis.[4] The necessity of differentiating such lesions is, therefore, of considerable practical importance.

The two patients presented in this communication were considered to have nonspecific myocarditis. Clinical and hemodynamic studies were performed in an attempt to establish criteria of diagnostic value. These studies failed to reveal findings which could be considered characteristic of myocarditis. The hemodynamic features defined in these two patients consisted of a pattern essentially identical to that originally described in constrictive pericarditis,[5-9] and which has since been shown to also occur in the presence of diffuse lesions of the endocardium[10] and myocardium.[11,12]

Thus, the hemodynamic pattern formerly considered to be of diagnostic value and characteristic of constrictive pericarditis has been demonstrated to occur in a large group of disease states, all of which have in common the property of impeding the normal filling of the ventricles and the normal ventricular ejection of blood.

CASE REPORTS

Patient 1, M. M., a 38-year-old Japanese woman, a farm laborer, was transferred to the Medical Service of Colorado General Hospital on April 22, 1955. She was asymptomatic until the age of 36 years, having delivered and raised six children without difficulty, and performed

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From the Cardiovascular Laboratory, Department of Medicine, University of Colorado School of Medicine, Denver, Colo.

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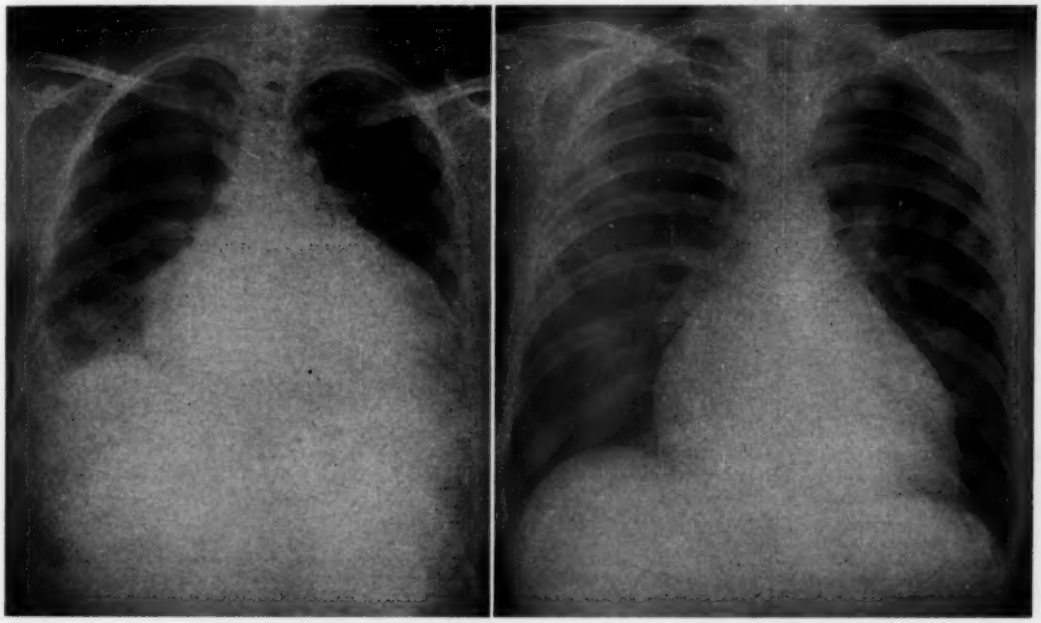
*Research Fellow of the American Heart Association.
†Deceased May 26, 1956.

heavy manual labor. During the latter part of the patient's seventh pregnancy there was an onset of swelling of the legs, orthopnea, and bouts of paroxysmal dyspnea. Delivery of a viable child was accomplished without difficulty, but the child died at the age of two months. Following this pregnancy the patient noted weakness, exertional dyspnea, and swelling of the legs. She was hospitalized for the first time five months after the birth of her seventh child and was told that she had rheumatic heart disease. Digitalization and salt restriction resulted in symptomatic improvement. Recurrence of symptoms took place five months later, requiring a second hospitalization.

At the age of 37 the patient began her eighth pregnancy. Progressive swelling of the legs and dyspnea upon exertion occurred throughout this pregnancy. There was intermittent response to digitalis and mercurial diuretics. Delivery was again uneventful, producing a normal child.



A. *B.*

Fig. 1.—Posteroanterior roentgenograms of (*A*) Patient 1, M. M., and (*B*) Patient 2, E. W.

Following delivery the patient continued to experience signs of congestive failure. The edema of her legs increased in magnitude and was accompanied by swelling of the abdomen. Dyspnea upon exertion became progressively severe but was not present at rest and was not associated with orthopnea. Anorexia was constant and vomiting occurred frequently. The patient was hospitalized and treated with salt restriction, digitalis, mercurial diuretics, and supplementary vitamins. Abdominal paracentesis resulted in the removal of 2,500 c.c. of clear, straw-colored fluid. There was little response to these measures, and the patient was transferred to this hospital.

The patient had subsisted on an inadequate diet for many years, which consisted mainly of rice imported from the orient. She had experienced recurrent episodes of pharyngitis and tonsilitis accompanied by fever during the past two years and received several courses of penicillin therapy.

Physical examination upon admission showed a chronically ill-appearing Japanese woman lying comfortably in bed. The systemic blood pressure was 100/90 mm. Hg and showed a 14 mm. variation in systolic level with deep breathing. The temperature was 36.4°C. and the respiratory rate was 20. The neck veins were distended when the patient was elevated to a 45-degree angle, but no venous pulsations were seen. Cyanosis and clubbing of the digits was not present, and neither petechiae nor telangiectases were noted. There was two-plus pitting edema of the ankles

and legs but no edema of the face or eyelids. The liver edge was palpable five fingerbreadths below the right costal margin. The spleen was not palpable. A considerable degree of ascites was present. The lungs were clear to percussion and auscultation.

The chest was normal in contour. No shocks nor thrills were noted. The apical impulse was palpable in the fifth intercostal space just beyond the midclavicular line. Percussion demonstrated the heart to be enlarged to one fingerbreadth beyond the midclavicular line in the fifth left intercostal space. Auscultation revealed that the second sound in the second left intercostal space was pure and not accentuated. No murmur was audible at the base of the heart. A Grade 2 blowing systolic murmur was audible midway between the left lower sternal border and the apex. A gallop rhythm was present at the apex. The first sound in this area was of normal intensity.

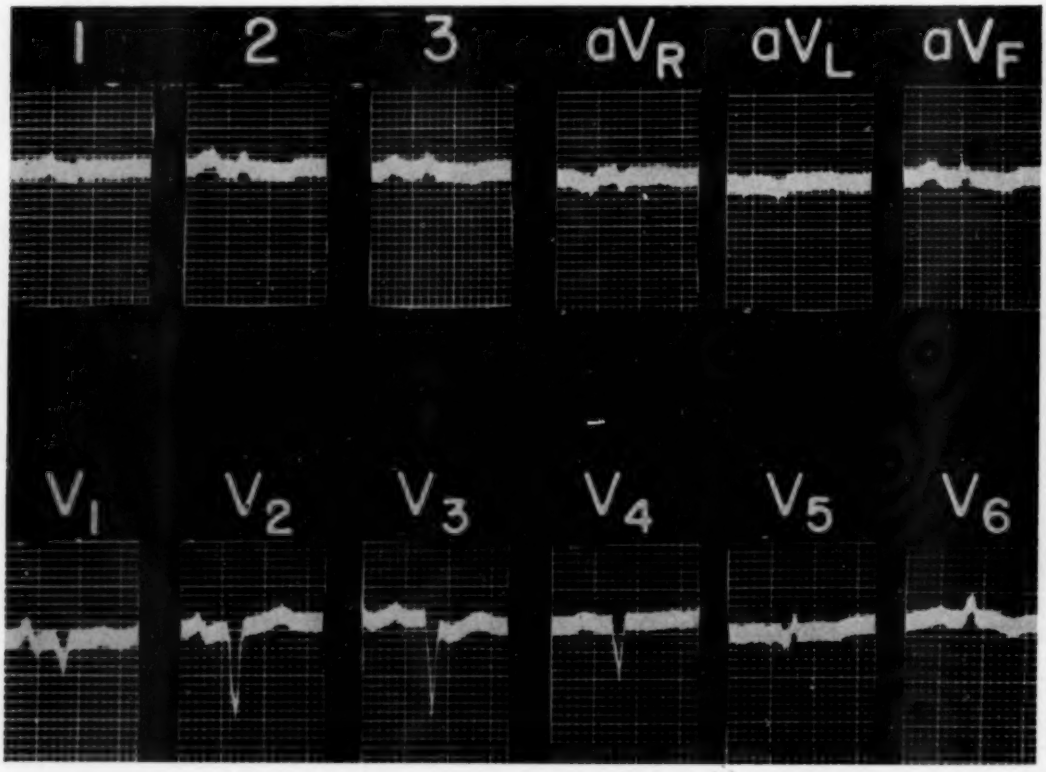


Fig. 2.—Electrocardiogram of Patient 1, M. M.

Laboratory Data.—Urine examination showed a specific gravity of 1.006 and albuminuria. There were 2 to 4 hyaline and 2 finely granular casts and 2 to 4 white blood cells per high power field. Blood examination showed 14.1 Gm. per cent hemoglobin and 8,650 W.B.C. consisting of 71 per cent polymorphonuclear leukocytes and 29 per cent lymphocytes. The hematocrit was 49. The initial prothrombin time was 19.5 seconds (29 per cent) and ten days later was 13.5 seconds (63 per cent). The blood glucose was 90 mg. per cent; the nonprotein nitrogen level was 37 mg. per cent. Serum chlorides were 103.7 and the carbon dioxide 22.7 meq. The total blood protein was 6.02 Gm. per cent, the albumin being 2.76 and globulin 3.26 Gm. per cent. The thymol turbidity was one unit. Total blood cholesterol was 137, the esters being 100 mg. per cent. The protein-bound iodine level was 6 and 9.1 micrograms per cent upon two determinations. Three L.E. cell preparations were reported as negative. Three blood cultures were negative. A Mantoux test (1/10,000 O. T.) was negative.

Fluoroscopy.—The costophrenic angles were clear, but the left costophrenic angle (Fig. 1,*A*) was difficult to visualize due to marked generalized enlargement of the heart, the left heart

border extending to the chest wall. The vascularity of the peripheral lung fields was normal. The right and left pulmonary arteries were enlarged, but the pulsations were within normal limits. The main pulmonary artery was prominent. There was marked enlargement of all of the heart chambers and the cardiac pulsations were generally diminished. The aorta and aortic knob were prominent. X-rays also showed generalized cardiac enlargement with a pleural effusion in the right and a questionable effusion in the left pleural space.

Electrocardiogram.—The electrocardiogram (Fig. 2) showed left axis deviation, a vertical electrical position, and a normal sinus rhythm. The rate was 90 per minute, P-R interval 0.18 second, and Q-T interval 0.36 second. The low voltage in the standard unipolar limb leads and in the chest leads was striking. The P waves were broad in II, III, and aV_F, and diphasic in V_1. The T waves were flattened or low in voltage in all leads. There was poor progression of R waves, and a broad Q and low R waves were present in V_5 and V_6.

Cardiac Catheterization.—The left atrial and right heart pressures were elevated (Table I, Fig. 3). The cardiac output was low and the A-V difference was greater than normal. There was but minimal thickening of the right atrial wall, as detected by placing the catheter tip against the lateral wall of this chamber. Presumably only a minimal amount of fluid was present in the pericardial space.

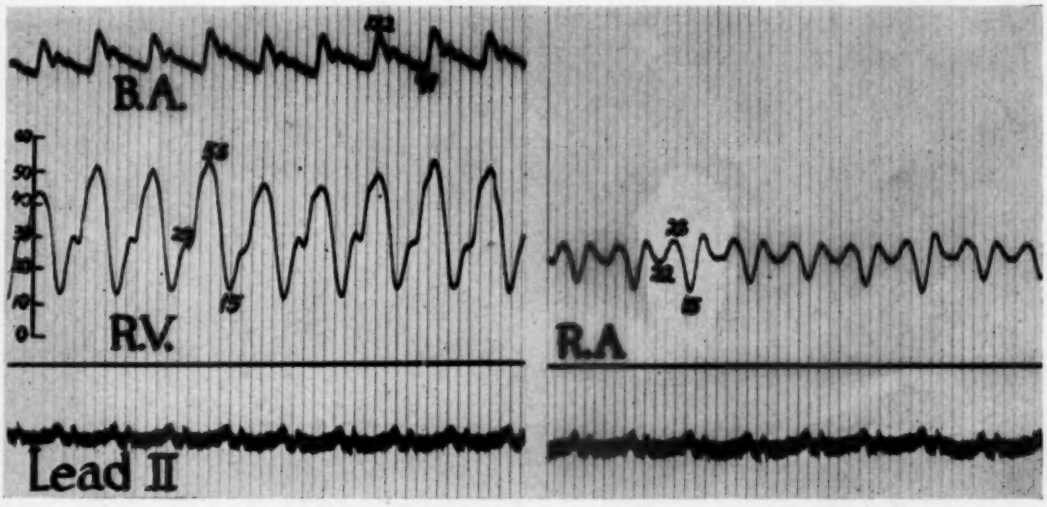


Fig. 3.—Right ventricular and right atrial pressure tracings of Patient 1, M. M.

Course.—The patient was put on bed rest; a high-calorie, high-vitamin, low-salt diet; and upon a maintenance dose of 0.5 mg. Digoxin per day. She felt tired and weak but could lie flat in bed comfortably and was never dyspneic at rest, nor orthopneic. She slowly gained in weight. Her temperature remained within normal limits throughout her hospital stay. Nausea and vomiting were persistent. During the evening of the eighteenth hospital day she felt nauseated and at times short of breath. She sat up in order to breathe better during one of these episodes and died suddenly and quietly a few minutes later.

*Post-Mortem Examination**.—Generalized edema was present. The peritoneal cavity contained 3,000 c.c. of straw-colored clear fluid, the left pleural space 200 c.c., and the pericardial sac 500 c.c.

The heart weighed 500 grams (Fig. 5). The epicardium was smooth, gray, and translucent. The left ventricle was 10 mm. and the right ventricle 3 mm. in thickness. The right atrium and right ventricle were dilated. The ventricular myocardium was pale tan, flabby, and several

*We are indebted to Robert L. Hawley, M. D., for the pathologic description and analysis.

TABLE I. PHYSIOLOGIC STUDIES IN TWO PATIENTS WITH CHRONIC MYOCARDITIS

PATIENT AGE SEX WT. B.S.	STATE	PRESSURES (MM. HG)									CARDIAC OUTPUT L./MIN.	CARDIAC INDEX L./MIN./M²	A-V O_2 DIFF. (VOL. %)	OXYGEN SATURATION (VOL. %)		O_2 CONS. (C.C. PER MIN.)
		PULMONARY CAP.	PULMONARY ARTERY		RIGHT VENTRICLE			RIGHT ATRIUM*		BRACHIAL ARTERY				BRACHIAL ARTERY	PULMONARY ARTERY	
			SYST./DIAST.	MEAN	SYST.	EARLY DIAST.	LATE DIAST.	PEAK	DIP							
1. M. M. 38 F. 151 lb. 1.74	Rest	30	54/39	44	52	14	28	28	18	127/101	1.74	1.16	10.02	94.8	40.9	176
	Exercise	32	54/34	40	54	16	32	36	20	125/93	3.32	1.53	12.50	92.2	24.7	288
2. E. W. 30 M. 100½ lb. 1.54	Rest	28	52/34	40	50	20	30	38	32	95/70	2.20	1.29	9.31	96.2	34.9	205
	Exercise	—	54/40	45	51	22	36	39	24	89/70	2.80	1.65	9.84	76.2	23.0	276

Wt. = weight, B.S. = body surface, Syst. = systolic, Diast. = diastolic, Diff. = difference, Cons. = consumption.
*Pressures at maximum, and at late diastolic dip.

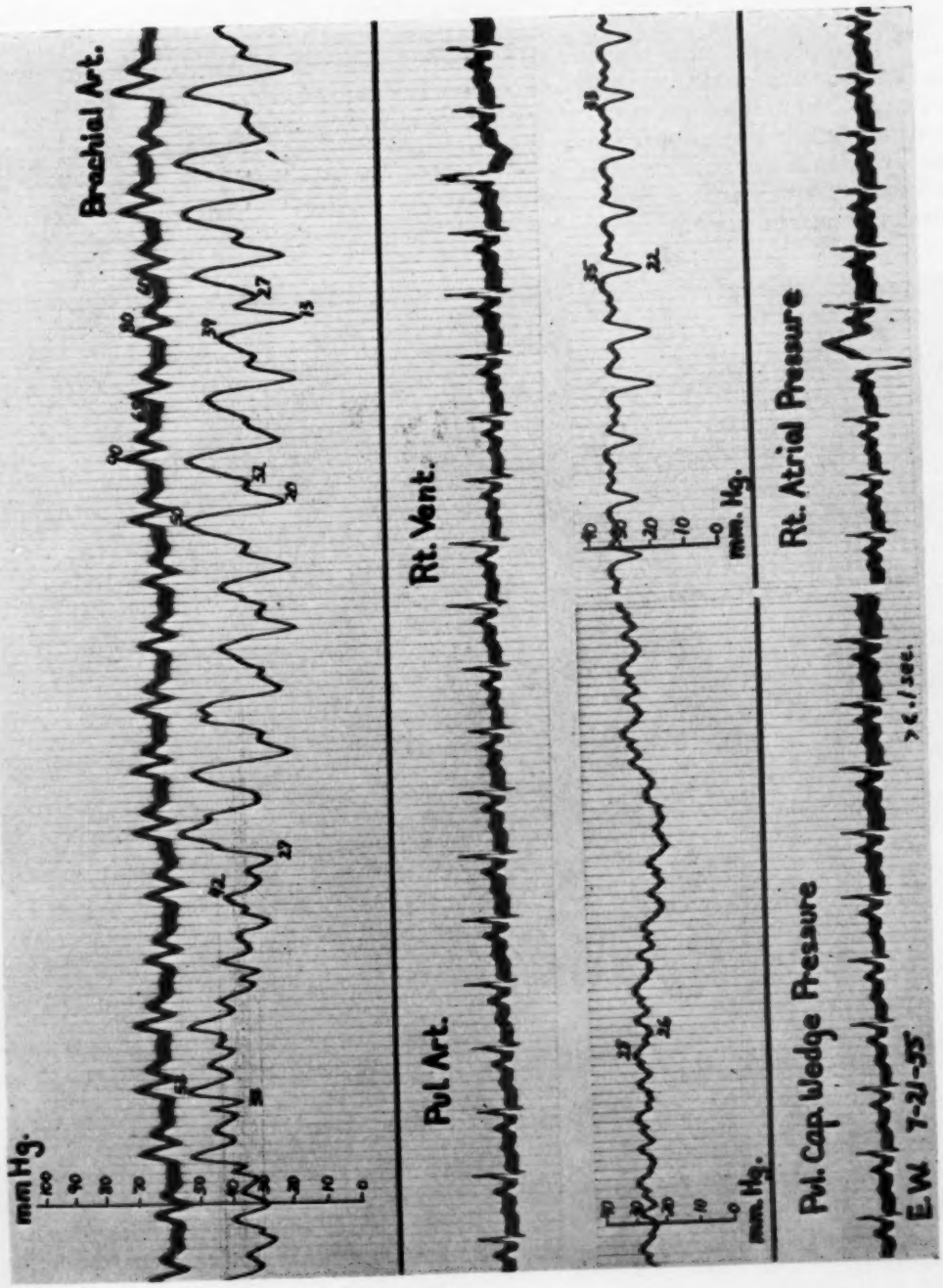


Fig. 4.—Pulmonary artery wedge pressure (left atrial), pulmonary artery, right ventricular, and right atrial pressure tracings of Patient 2, E. W.

softened areas were visible. This mottling was particularly prominent in the interventricular septum. The endocardium was dull and thickened in the left ventricle. A mural thrombus was present at its tip. The endocardium of the right ventricle was smooth, gray, and thickened. The foramen ovale was probe patent. Valve circumferences were: tricuspid 13 cm., pulmonic 8.5 cm., mitral 11 cm., and aortic 7 cm. The coronary ostia and arteries were patent and elastic. The intima was smooth. A recent pulmonary infarct was seen in the lower lobe of the right lung. Microscopic examination (Fig. 6) showed the myocardial fibrils of the left ventricle to be widely separated and the widened interstitial spaces to contain a finely granular eosinophilic material. Several discrete foci showed disappearance of the myocardial fibers without destruction of the stroma. Capillaries and veins were engorged. In other areas of the left ventricle the myocardial fibers were distorted, separated by increased collagen that was infiltrated by a few lymphocytes, scattered plasma cells, and macrophages. The sarcoplasm of the myocardial fibers was frayed.

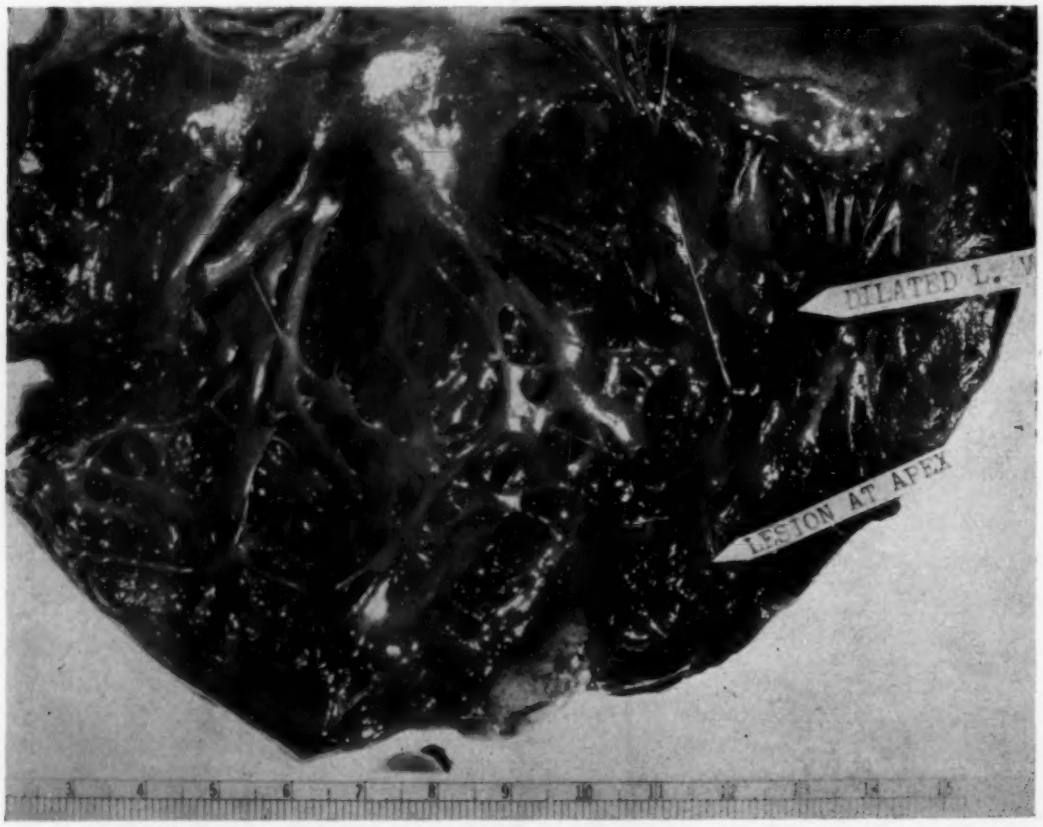
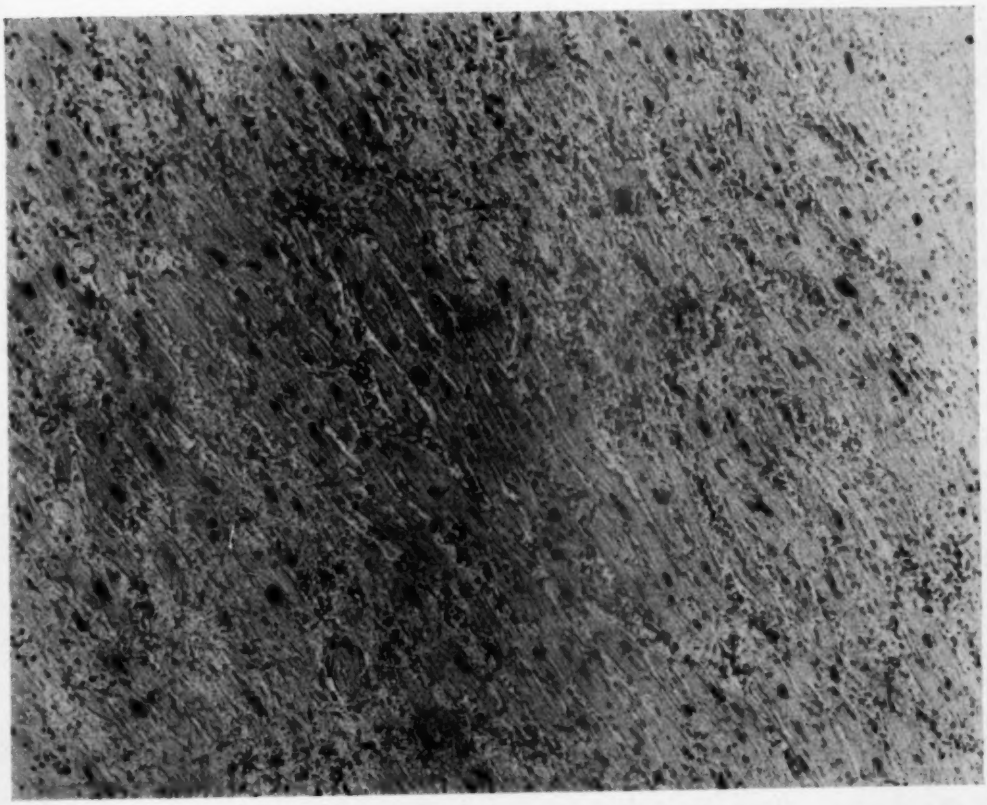


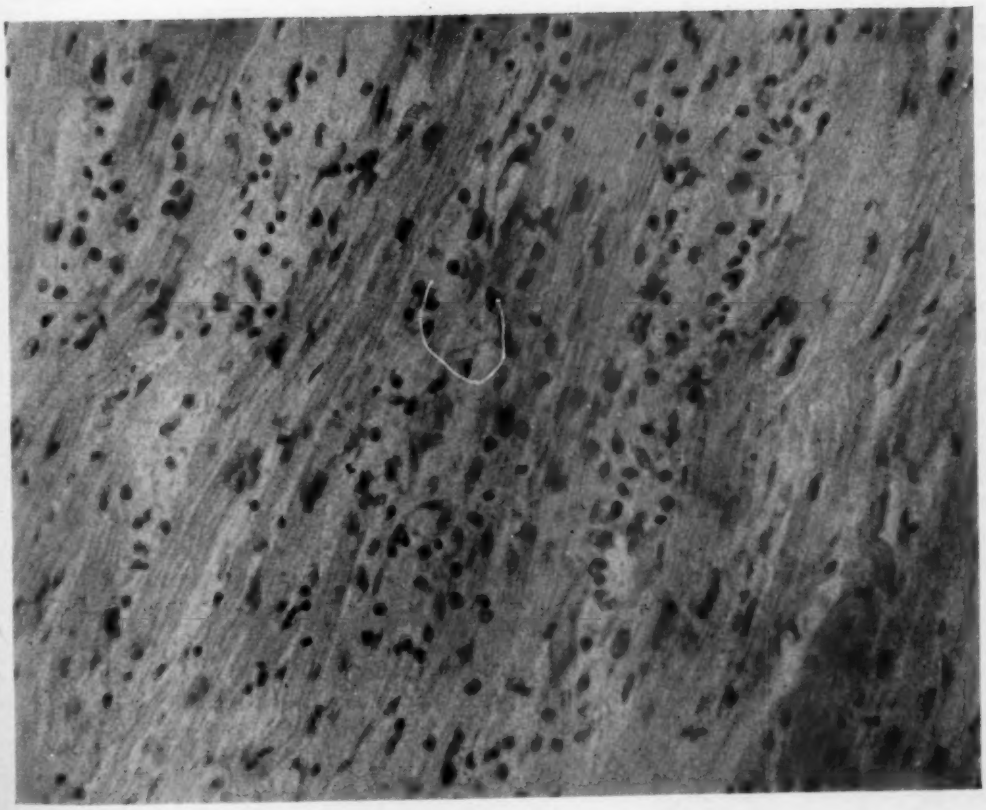
Fig. 5.—Gross heart of Patient 1, M. M.

In the right ventricle scattered lymphocytes and neutrophilic leukocytes infiltrated the interstitial tissue. The most severe changes were in the posterior wall of the right ventricle. The left atrium showed an infiltration by lymphocytes, macrophages, neutrophilic leukocytes, and a few Aschoff cells.

Conclusion From Post-Mortem Examination.—None of the essential stigmata of a collagen disease were present. The endocardial changes (slight thickening) were thought to be due in part to the stretching and injury caused by the dilation of the heart chambers. The combination of old fibrous scars, increased inter-



B.



A.

Fig. 6.—*A* and *B*, Microscopic sections through left ventricle of Patient 1, M. M.

stitial connective tissue and edema, and profound acute and chronic inflammatory cell infiltrations suggested chronic and recurrent myocarditis, probably secondary to upper respiratory infections.

Comment.—The diagnosis, chronic myocarditis, was considered justified by the definite histologic evidence of inflammation of the myocardium and by the prolonged clinical course with recurrent episodes of cardiac failure over a two-year period. No definite etiology was apparent. During the hospital course several observers considered the possibility of a massive pericardial effusion. A diagnostic pericardial aspiration was planned but was not accomplished prior to the patient's death. Entities such as beriberi heart disease, poststreptococcal myocarditis, post-partum myocarditis, and myocarditis associated with collagen disease were all considered. It was felt that the poor diet of the patient and the several episodes of fever and pharyngitis were factors in the etiology of the chronic myocarditis.

Patient 2, E. W., a 30-year-old, white man, a truck driver, was admitted to the Medical Service of Denver General Hospital on July 5, 1955, complaining of shortness of breath. He had been in good health until nine months prior to admission at which time shortness of breath on exertion was first noted. Six months prior to admission swelling of the legs and of the abdomen occurred. These symptoms forced the patient to stop work and seek medical attention. Digitalization was accomplished and mercurial diuretics were given with a resulting decrease in the edema and exertional dyspnea. The patient attempted to return to work but was forced to stop after one day. He discontinued the medications and again noted progressive swelling of the legs and abdomen and progressive limitation in exercise tolerance due to dyspnea and fatigue. A twenty-pound weight gain was observed one month prior to admission. Exercise tolerance was reduced to walking a few feet. The patient slept on two pillows and in addition elevated the head of the bed. He awoke frequently at night with shortness of breath and was forced to sit erect. Two weeks prior to admission a pruritic skin lesion appeared over the entire body.

The past history was significant in that he was rejected for Army duty in 1941, because of "an enlarged heart." He was accepted by the Merchant Marine and served actively at sea duty for five years as a cook. The patient then performed heavy labor from 1946 to the onset of the present illness. There was no history suggesting episodes of rheumatic fever or venereal infections. A moderately heavy alcoholic intake was described for the past twelve years with an increased consumption during the present illness.

Physical Examination.—The initial examination revealed an acutely ill man sitting up in bed breathing at a rapid rate. A pustular dermatitis with excoriation was present on the trunk, face, and upper extremities. The neck veins were distended and pulsating with the patient erect. The peripheral pulses were equal in all extremities, were weak in quality, and demonstrated a change in volume relative to respiration. The blood pressure was 105/80 mm. Hg during inspiration and 90/70 during expiration. Palpation of the precordium revealed a hypodynamic cardiac impulse. The area of cardiac dullness was increased to the right and to the left by percussion. Auscultation revealed a regular rhythm at a rate of 120. The heart sounds were slightly decreased in intensity over the entire precordium. The second heart sound was greater in intensity in the pulmonic than in the aortic area. A Grade 2, blowing, systolic murmur was audible at the apex with transmission to the left axilla. An early diastolic sound was present at the apex producing a gallop rhythm. The lungs were clear to auscultation and percussion. The abdomen was distended and there was evidence of free peritoneal fluid. The lower margin of the liver was palpable 6 cm. below the right costal margin. Massive pitting edema was present in the lower extremities. The body weight was 178 pounds.

Laboratory Studies.—The hemogram was normal throughout the hospital admission. Urinalysis on admission showed albuminuria, microscopic hematuria, and hyaline casts. Subsequent urinalyses were normal. Renal function studies were within normal limits. Serologic tests for

syphilis were negative and a lupus erythematosus preparation was negative. Liver function tests on admission were abnormal. The bromsulphalein retention was 42 per cent in 45 minutes. The total serum bilirubin was 2.8 mg. per cent, the total cholesterol 97 mg. per cent, with 48 mg. per cent esters. The total protein level was 7.4 Gm. per cent. There was marked regression in these abnormal values during hospitalization. The bromsulphalein retention was only 3 per cent in 45 minutes by the third week. The blood sedimentation rate was 11 mm. Microscopic examination of a skin biopsy obtained surgically revealed nondiagnostic abnormalities which included fibrinoid degeneration in the dermis and vacuolization in the basal cells.

Electrocardiogram.—The electrocardiogram showed a sinus rhythm with a tachycardia ranging from 100 to 112 on three tracings. The electrocardiographic intervals were within normal limits and showed no change on serial tracings. Fairly frequent premature ventricular contractions were present in all tracings. A pattern of left ventricular hypertrophy was evidenced by an S wave 35 mm. in depth in Lead V_2 and an R wave 20 mm. in amplitude in Lead V_5. The T waves were inverted in leads reflecting the left ventricle.

Fluoroscopy.—Fluoroscopic and roentgenographic examination of the chest revealed increased vascularity of the lung fields and considerable cardiac enlargement with a globular configuration (Fig. 1,*B*). There was a decreased amplitude of pulsations along all heart borders. The superior vena cava shadow was prominent. Serial films showed clearing of the lung fields and a slight decrease in the overall heart size. Bedside methods showed a venous pressure of 26.0 cm. of water with a prompt rise to 33.5 cm. on right upper quadrant compression. The arm-to-tongue circulation time with Decholin was 48 seconds. Cardiac catheterization was carried out on July 22, and the findings are summarized in Table I. The catheter tip could be advanced very close to the margin of the right atrial silhouette, indicating no significant thickness of the pericardium and, therefore, no fluid in the pericardial space.

Course in Hospital.—The patient was considered to present clinical findings suggestive of a large pericardial effusion. A diagnostic pericardial aspiration was, therefore, attempted on July 12, 1955. A needle was introduced beneath the xiphoid and slowly advanced upward and backward with constant suction applied. No pericardial thickening or pericardial fluid was encountered. Nonspecific myocarditis was then considered to be the most likely diagnosis.

Therapy consisted of bed rest and a diet low in sodium with a high caloric value and with supplemental vitamins. Mercurial diuretics were administered for the first two weeks of hospitalization. The body weight fell from 174 pounds to 146 pounds and the patient became essentially asymptomatic at rest upon this regimen. Abdominal paracentesis was followed by a reduction in weight to 142 pounds. Digitalization was accomplished with digitalis leaf at the beginning of the fourth week of hospitalization. A slow further weight loss to 134 pounds occurred over the next two weeks. The venous pressure fell to a level of 160 mm. of water at this time. The patient was discharged on Aug. 15, 1955. He was asymptomatic if he limited his activities to mild physical exertion. The patient moved from this area and was not available for personal follow-up. Written communication, however, revealed no change in symptoms through December, 1955.

Comment.—The diagnosis of chronic nonspecific myocarditis was established in this patient only by a process of exclusion. No common cause of cardiac disease could be identified in this relatively young man. A number of uncommon lesions were considered. Nutritional heart disease was excluded on a basis of the physiologic evidence of a low cardiac output and the lack of response to thiamine. No evidence was found to suggest a form of collagen disease, primary amyloidosis, or any other systemic disease that might have involved the myocardium. The protracted clinical course and the persistence of gross cardiomegally at the time of discharge from the hospital excluded the forms of acute myocarditis that may accompany viral diseases.

DISCUSSION

Clinical Aspects of Nonspecific Myocarditis.—The clinical data from these two patients illustrated the difficulties which may be encountered in differentiating a large dilated heart in failure from an enlarged cardiac silhouette resulting from pericardial effusion. A number of features were present in these patients which have been described as characteristic or suggestive of pericardial disease.[4] Both patients demonstrated a diminished amplitude and a marked respiratory variation of the radial pulse, the so-called pulsus paradoxicus. A pattern of "right heart failure" was dominant, with massive edema, ascites, hepatomegally, and impaired hepatic function. The lack of orthopnea was striking in Case 1. There was no increased precordial activity noted by palpation in either patient, and the heart sounds were diminished in intensity in Case 2. A globular cardiac silhouette with diminished activity was present upon fluoroscopy. The electrocardiogram in Case 1 was similar to those reported in pericardial disease.[4]

This overlapping of the clinical features of an enlarged heart in failure and pericardial disease indicates that no single clinical sign or group of signs offers a reliable basis for the differential diagnosis of these two entities in the individual case. Recourse to specific diagnostic measures may often be necessary to aid in establishing the diagnosis. Direct aspiration of a significant quantity of fluid or exudate from the pericardial cavity affords the most conclusive evidence. Demonstration of a significant increased distance from the inner margin of the right atrial cavity to the outer border of the atrial silhouette is another form of precise diagnostic evidence. This may be accomplished by filling the right atrium with contrast media or by placing the tip of a cardiac catheter against the lateral margin of the right atrial cavity. Exploratory thoracotomy may at times be necessary to be absolutely certain of the absence of pericardial constriction since accurate diagnosis may not be possible by any other means.[10,13] An additional confusing factor may be the occurrence of minor degrees of pericardial effusion as a secondary phenomenon in severe cardiac failure as was demonstrated by the first patient.

Hemodynamic Aspects of Nonspecific Myocarditis.—The data obtained at cardiac catheterization (Table I) was remarkably similar in the two patients. The general hemodynamic picture was that of severely impaired myocardial efficiency. The cardiac output was reduced to approximately one-third of normal. The peripheral oxygen extraction was increased with a resulting arteriovenous oxygen difference of more than twice the average normal value. The right atrial and right ventricular diastolic pressures were elevated to high levels. Similar high pressure levels were assumed to be present in the left heart chambers on the basis of the elevated pulmonary artery wedge pressure level. The pulmonary arterial and right ventricular systolic pressures were only slightly elevated, to a level proportionate to the elevated pulmonary artery wedge pressure. The pulse pressure in the pulmonary artery and in the systemic arterial system was narrowed, reflecting the low cardiac output.

The response to exercise in these patients demonstrated an almost total lack of cardiac reserve (Table I). The absence of increase in cardiac output or pulmonary arterial pressure following exercise suggested that compensatory

cardiovascular mechanisms had been utilized to the fullest even in the resting state. An increase in peripheral oxygen extraction was noted during exercise with the mixed venous blood oxygen saturation levels falling to 24.7 and 23.9 per cent, respectively. The pressures in the atria and ventricles in diastole showed a further increase above the resting levels. The decrease in the peripheral arterial oxygen saturation in Case 2 was not readily explained. Mechanisms such as a right-to-left shunt through a dilated foramen ovale or an impairment of oxygen diffusion at the alveolocapillary membrane level were considered, but these remained conjectural. The general hemodynamic pattern was thus of value in documenting the severity of the cardiac impairment and in excluding such lesions as congenital cardiovascular defects, high cardiac output states, and primary pulmonary disease.

The details of the right heart chamber pressures were of considerable interest (Figs. 3 and 4). The right ventricular pressures showed a slight-to-moderate elevation during systole followed by a sharp dip in early diastole. This early diastolic level represented the period of lowest pressure in the ventricle during the cardiac cycle but was nonetheless considerably elevated (15 mm. Hg) above normal levels. An abrupt rise to a higher level (28 to 30 mm. Hg) then occurred and was maintained throughout the remainder of diastole. The level of the end-diastolic pressure constituted more than 60 per cent of the right ventricular systolic pressure in both patients. The right atrial pressure contours were characterized by a high-pressure level interrupted by two dips in each cardiac cycle, with a resultant "M" or "W" configuration. The first of the pressure declinations occurred during early ventricular systole; the second and larger dip occurred in early ventricular diastole, corresponding to the simultaneous decrease in the right ventricular pressure. The mean right atrial pressure levels approached the diastolic pressure level in the pulmonary artery and the late diastolic pressure level in the right ventricle.

Comparison With Hemodynamic Patterns in Other Disease States.—The magnitude of the right heart pressure derangements in these patients far exceeded that described in the usual instance of congestive failure associated with known entities such as hypertensive arteriosclerotic or valvular heart disease.[14] The pressure tracings in these two patients showed features which clearly distinguished them from those seen in free tricuspid valvular insufficiency[15] or stenosis.[16]

However, the pattern found in these two patients with myocarditis was essentially identical to that which has been demonstrated to occur in a group of other entities which impair myocardial efficiency. It was first observed to be associated with constrictive pericarditis, as has been described by Hansen,[5] and others.[6-9] Patients with constrictive pericarditis operated upon at this hospital demonstrated an identical hemodynamic picture. These unusual right heart chamber pressure patterns were originally considered to be relatively specific for pericardial disease. The demonstration of the characteristic pattern by cardiac catheterization was thought to constitute a diagnostic aid in selecting patients for pericardiectomy. However, additional experience here and elsewhere has since demonstrated a lack of specificity of this laboratory finding. For

example, a patient with a clinical picture indistinguishable from constrictive pericarditis was demonstrated to show this characteristic right heart chamber pressure pattern. Exploratory thoracotomy was performed and a normal pericardium was found. Post-mortem examination six months later showed severe generalized subendocardial fibroelastosis.[10] Burwell has presented studies of patients with myocardial fibrosis secondary to coronary atherosclerosis which showed the same pressure phenomena.[11] A case reported by Hetzel clearly demonstrated that this pattern occurs in patients with cardiac amyloidosis.[12] A report has recently appeared showing the same phenomenon in a patient with a thoracic cage deformity of the pectus excavatum type.[17] Thus, instead of affording specific diagnostic aid this "characteristic" hemodynamic pattern is actually common to the disease states comprising the group for differentiation.

The pattern can no longer be considered of diagnostic value except in this very broad sense. It is present in circumstances where the normal relaxation and filling of the ventricles is restricted and the normal contraction of the ventricles and the ejection of blood is impaired. These seemingly widely varied disease states involving the endocardium, myocardium, pericardium, and at times extracardiac structures all impede normal ventricular function.

It may be presumed that other disease states will be shown to demonstrate these same pressure phenomena. The pattern is likely to occur in the collagen group of diseases, particularly in scleroderma heart disease. It may well occur in the fibrotic myocardial lesions associated with neurologic diseases, such as Friedreichs ataxia or with hemochromatosis. It is certainly likely to be found in the infiltrative myocardial lesions such as glycogen storage disease, severe fatty infiltration, and conceivably with diffuse neoplastic infiltration of the myocardium. Thoracic cage deformities other than the pectus excavatum type may also be accompanied by this physiologic pattern.

SUMMARY AND CONCLUSIONS

1. Clinical and hemodynamic studies in two patients with chronic myocarditis have shown a pattern essentially identical to that occurring in constrictive pericarditis.

2. This hemodynamic pattern is, therefore, not pathognomonic or even characteristic of any single entity but is common to a group of disease states which have the property of impairing myocardial function. These entities may diffusely involve the pericardium, myocardium, or endocardium, and may occur external to the heart. This pattern is, therefore, of general and not of specific diagnostic value.

SUMMARIO IN INTERLINGUA

Duo patientes con chronic myocarditis nonspecific esseva studiate per methodos clinic e hemodynamic in un essayo de establir criterios de valor in le diagnose differential. Le patientes presentava un syndrome de cardiomegalia, disfallimento congestive refractori al therapia, e absentia de etiologia specific, de maniera que le differentiation de iste condition ab lesiones apparentemente simile sed cedente al therapia esseva imperative. Le configuration hemodynamic

exhibite per iste duo patientes esseva essentialmente identic con illo que es trovate in casos de pericarditis constrictive. Il ha essite trovate (1) que iste configuration se presenta in un numero de lesiones diffuse que involve le pericardio, le myocardio, e le endocardio, e (2) que su valor diagnostic es consequentemente general e non specific.

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HEMODYNAMIC CHANGES DURING "FLUSH" IN CARCINOIDOSIS

(The Carcinoid Syndrome)

Åke H. Thorson, M.D.

Malmö, Sweden

THE carcinoid syndrome was first recognized a few years ago,[1-6] but has attracted a good deal of interest, and is of both academic and practical importance. It has, as yet, been found only in cases with extensive metastases. The history of its recognition has already been reported in detail.[5]

In advanced cases the morphologic changes include not only one or more intestinal carcinoid tumors (argentaffinomas) with metastases to lymph nodes, liver, and other organs, but in addition "sclerotic" changes may occur in the very small arteries and precapillary arteries; and the small cutaneous veins, especially those of the face, may be wide and tortuous. Sclerosis of the valvular and mural endocardium, especially in the right half of the heart, may occur with pulmonary and/or tricuspid stenosis and regurgitation, and consequent myocardial hypertrophy or dilatation.

The most conspicuous symptoms are vasomotor disorders of the skin, and hyperperistalsis of the digestive tract with sudden attacks of diarrhea, borborygmi, and intermittent abdominal pain. The cutaneous vascular symptoms consist of transient but often intense flushing of a peculiar type, known as "phenomenal flushing," and of intermittent patchy cyanosis. The flushes are sometimes accompanied by bouts of respiratory distress. As the disease advances, frank symptoms of cardiac involvement may appear. In 1954, Thorson and associates[5] published a survey of seven cases with all of these symptoms and nine with only some of them (one patient described by Millman,[7] as well as by Gold and Grayzel,[8] had been missed). Since then, a number of additional cases have been reported by several authors,[9-24] and the syndrome does not seem to be extremely rare. These additional cases showed essentially the same type of symptoms and signs as those described in the surveys by Waldenström and Ljungberg,[25] and Thorson and associates.[5]

It was suggested[5] that the vasomotor disorder, the hyperperistalsis, and the bouts of dyspnea might be due to a pronounced response of smooth muscle to one or more endogenous substances liberated from the tumor into the blood stream, probably 5-hydroxytryptamine (serotonin, enteramine, thrombocytin). This assumption has been strongly supported by the isolation of 5-hydroxytryptamine in considerable quantities from both primary and metastatic carcinoids by

From the Department of Medicine (Head: Professor Jan Waldenström), University of Lund, Malmö General Hospital, Malmö, Sweden.

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Lembeck,[26,27] by the finding by Pernow and Waldenström[28] of high levels during flush of a substance, physiologically identified as 5-hydroxytryptamine in blood from two patients with the carcinoid syndrome, and by the demonstration by Page and associates[29] of abnormally high daily output of 5-hydroxyindol acetic acid, a metabolite of 5-hydroxytryptamine, in the urine of three patients with metastasizing carcinoids. This has since been amply verified.[20-24,30-36] Dockerty and Scheifley[16] have reported a case with a testicular carcinoid tumor, probably metastatic, in which manual compression of the tumor immediately produced a flush, exactly mimicking the spontaneous flushes in this patient. After extirpation of the testicular tumor, the tendency to flush disappeared. It is, thus, established that the carcinoids contain and liberate considerable amounts of 5-hydroxytryptamine, an endogenous substance with a strong action on smooth muscle, and, secondly, that flushes can be induced by gushes of pharmacologically active substances from the tumor. Although much argues for 5-hydroxytryptamine by itself being responsible for the phenomenal flushing in patients with carcinoid tumor, the co-action of other substances, either released from the tumor itself[29] or released peripherally by gushes of 5-hydroxytryptamine, cannot be excluded at present.

This paper is concerned with an investigation of the hemodynamic pattern during flush in patients with the "carcinoid syndrome," studied during long periods of observation in hospital. Special attention was directed to changes in the distribution, rate of flow, and pressure of the blood, as well as to the degree of contraction and relaxation of the vessels in various parts of the circulatory system in different stages of the cutaneous flush.

MATERIALS AND METHODS

Materials.—The material consists of four patients, one man and three women, aged 57, 43, 48, and 57, with metastasizing carcinoid of the small intestine, increased output of 5-hydroxyindol acetic acid, diarrhea, and typical episodic flushing. Patients E.P. and S.H. were included in an earlier paper, and V.M. and H.B. are now added.

Apparatus.—The following apparatus were used: The Elema Klinik 5-channel electrocardiograph with the Elema piezo-electric phonocardiographic unit; the Elema piezo-electric displacement ballistocardiograph (the ballistocardiograph and the technique used have been reported elsewhere[37]); several models of roentgenographs and fluoroscopes. For special studies an apparatus designed to expose teleroentgenograms with variable delays from the R-peak in the electrocardiograms was used, permitting a closer study of variations in heart volume. This apparatus was constructed and manufactured by the Elema Company, Sweden, which also manufactured the angiocardiographic film transmitter (model Gidlund), used in some studies. The Riva Rocci cuff was used for blood pressure studies.

Methods.—During different stages of the flush phenomenon electrocardiograms, phonocardiograms, and ballistocardiograms were recorded, radiographic and fluoroscopic examinations were carried out, the brachial blood pressure was measured with half-minute intervals, and changes in the quality of the radial pulse as well as in the compressibility of the radial artery between the pulse waves were studied.

RESULTS

It was pointed out in a previous paper[5] that the cutaneous flush usually runs a characteristic course in which, generally speaking, a definite sequence of events, sometimes well defined, can be recognized, so that, arbitrarily, the cutane-

TABLE I. CIRCULATORY PATTERN DURING FLUSH, STAGE 1, FOUND IN E.P., S.H., V.M., AND H.B.

	FINDINGS	TENTATIVE INTERPRETATION
The skin	Increasing reddening and burning	Local dilatation of precapillary arteries and capillaries. Brief pooling of blood in the capillaries
The pulse	Irregular and weak	Small stroke volumes, low cardiac output
Auscultation and phonocardiography	Decreased sounds and murmurs	
Fluoroscopy	Weak and small pulsations	
Ballistography	Low amplitudes	

ous flush can be divided in a number of successive stages. The color changes during flush in the two patients now added were of the same type as those seen in the former series.

In the present investigation, alterations in the central hemodynamics were found to be temporally related to the transitions between the various stages of the cutaneous flush. They are described stage by stage.

Stage 1 (*Table I*).—This stage usually lasted about 20 seconds. In the skin, it was characterized by the onset and progression of reddening and burning, usually commencing in the face and spreading over the trunk and extremities. A few seconds after the onset, the first and second heart sounds as well as any abnormal heart sounds and murmurs became fainter or disappeared (Fig. 1,*B*). The heart rhythm was sometimes irregular, bursts of rapid beats alternating with

TABLE II. CIRCULATORY PATTERN DURING FLUSH, STAGE 2, FOUND IN E.P., S.H., V.M., AND H.B.

	FINDINGS	TENTATIVE INTERPRETATION
The skin	Red and hot	Dilatation of a major part of the precapillary arteries and capillaries of the skin. Low vascular resistance in the skin
The pulse	Celer et altus, mostly tachycardia	Large stroke volumes, high cardiac output. Low vascular resistance generally
Blood pressure	High systolic and pulse pressures	
Auscultation and phonocardiography	Loud sounds and murmurs, abnormal sounds	
Fluoroscopy and roentgenograms	Large and whippy pulsations of the right margin and the pulmonary conus. Increased volume	
Ballistography	High amplitudes	

slow beats, but the number of beats per 15 seconds was usually normal or only slightly increased, and the impulse formation occurred in the sinoauricular node in these patients. The number of blood pressure determinations made in this brief stage was not large enough to permit any valid conclusions. Fluoroscopy showed that the heart contractions suddenly diminished almost immediately after the appearance of the flush and were then barely discernible for the rest of this stage. The I, J, and K waves in the displacement ballistogram also rapidly diminished soon after the onset of the flush, and within a couple of seconds became low and rounded, and remained so throughout the rest of the stage. No signs of venous congestion were observed, and, apart from variations in heart rate, the electrocardiographic pattern was essentially the same as before, and remained unaltered throughout the flush.

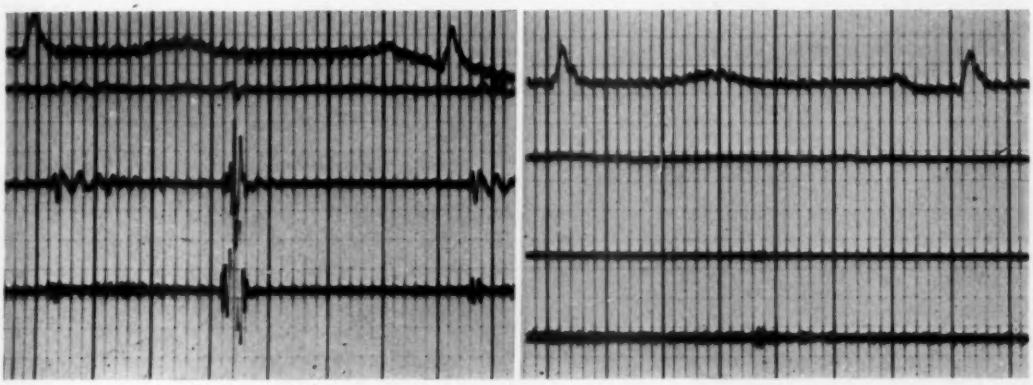


Fig. 1.—S.H., second right intercostal space. *A* shows a phonocardiogram (amplification 1/10) obtained before flush, and *B* shows another (amplification 1/10) obtained during Stage 1. The heart rate did not change, but the sounds became very weak. This was also registered repeatedly in E.P., and was not due to technical errors.

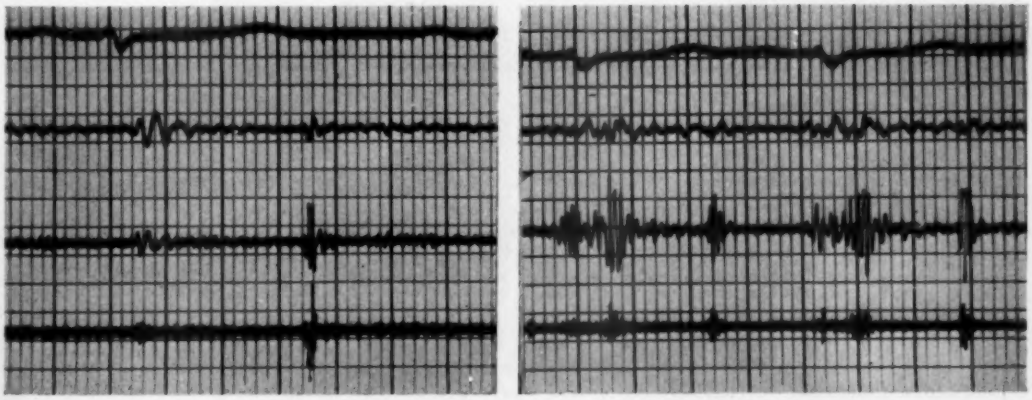
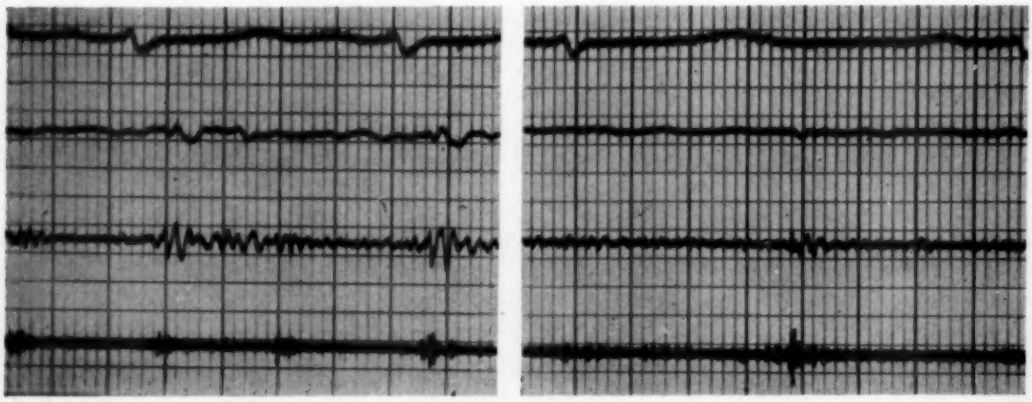


Fig. 2.—E.P., third left intercostal space. *A*, before flush. *B*, during Stage 2. (N.B. amplification before flush 1/5 as against 1/20 during Stage 2). The heart rate increased, the first and second sounds became strong, and a presystolic sound appeared.

Stage 2 (*Table II*).—Stage 2, which commenced when the flush and the sensation of burning was fully developed, usually lasted one or two, and occasionally several minutes.

At the beginning of this stage, the heart sounds, especially the first sound, markedly increased, and abnormally strong presystolic sounds, early systolic and diastolic sounds, as well as systolic and probably also presystolic murmurs either appeared, or became stronger than be-

fore the onset of flush* (Figs. 2,*B* and 3,*A*). Usually, but not always, the heart rate increased to, at most, 160 beats per minute. (In one subject, V. M., a decrease was noted occasionally.) There was sinus rhythm. The radial pulse was fast and large, and in E.P. the carotid arteries were seen to pulsate vigorously and with large amplitudes. The systolic arterial blood pressure sometimes increased moderately but distinctly, while the diastolic pressure (as determined at the disappearance of the arterial sound) persisted practically unchanged, so that the pulse pressure increased. This, however, was not a regular feature; it appeared only in severe flushes, and even then not always. Sometimes both the systolic and diastolic pressures persisted unchanged.



A. *B.*

Fig. 3.—E.P., second right intercostal space. *A*, during Stage 2. *B*, during Stage 3. (N.B. amplification during Stage 2, 1/20 as against 1/2 during Stage 3). The heart rate was rapid in Stage 2, but normal in Stage 3, during which the heart sounds and murmurs were weak.

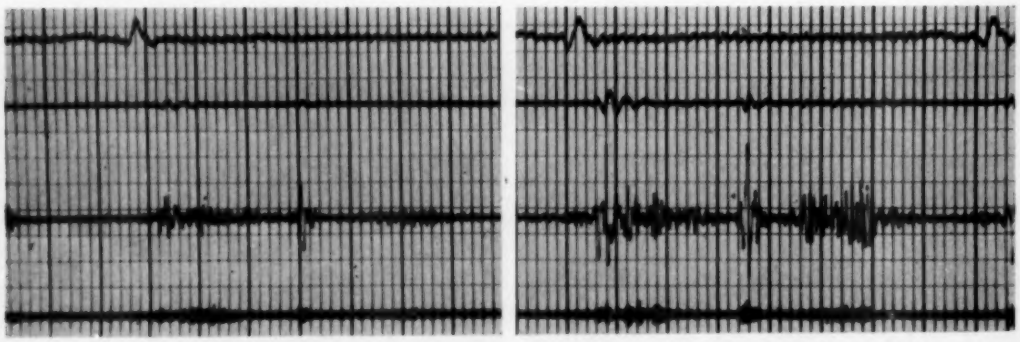


Fig. 4.—H.B., fifth left intercostal space at the sternal border. The two sections were cut from a phonocardiogram obtained during the rapid regression of cyanosis at the end of a flush. The microphone and the amplifier were not altered in any way. The original tracing showed a gradual increase of the sounds and murmurs. The interval between the two cuttings shown was 6 seconds.

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*In S.H., H.B., and V.M. harsh systolic murmurs, already present in flushfree intervals, increased in Stage 2. In E.P. a similar murmur was present only in Stage 2. The murmurs occupied the first two thirds or three fourths of the systole and were best heard near the xiphoid junction or in the third and second left intercostal spaces near the sternal border. Phonocardiograms confirmed the auscultatory findings. Also, a number of additional heart sounds were strongest in or appeared only in Stage 2. Thus, a short burst of oscillations suggesting a sound was inconstantly found some 0.12 second after the main deflections of the first sound in E.P., S.H., and H.B., and similar oscillations occurred in mid-diastole in E.P. and H.B. Short presystolic sounds of low frequency began 0.09 to 0.12 second after the beginning of the P wave in all four patients. Sometimes, presystolic oscillations suggesting a murmur were apparent in addition. When strong, the abnormal sounds were clearly audible as gallop sounds.

Three of the patients experienced severe palpitations throughout Stage 2, during which fluoroscopy showed that the heart contractions, especially at the margin of the right ventricle and the pulmonary conus, suddenly increased at the onset of the stage and became large and whippy and persisted so during the entire stage. The I, J, and K waves in the ballistograms became high and peaked within a couple of seconds of the onset of the stage, and remained so until the end of the stage, no matter whether the heart rate increased or not (Figs. 5,*B* and 7,*B*).

The Transition to Stage 3.—The transition to Stage 3, the cyanotic stage, was usually gradual, but sometimes rapid. The transition was characterized by decreasing erythematous discoloration and by the appearance of mottled or patchy cyanosis, which was sometimes intense. Also, peculiar yellow-red patches and blanched patches were frequently seen during the end of Stage 2 and the beginning of Stage 3. Sometimes, they changed form and migrated before they disappeared. At the transition, the palpitations disappeared, all heart sounds and murmurs became fainter, any increase of the heart rate during Stage 2 decreased, and the radial pulse became weak or even not palpable, but the radial artery felt distended, and in E.P. the carotid arteries were sometimes very prominent and tender to palpation. When the cyanosis was severe, E.P.

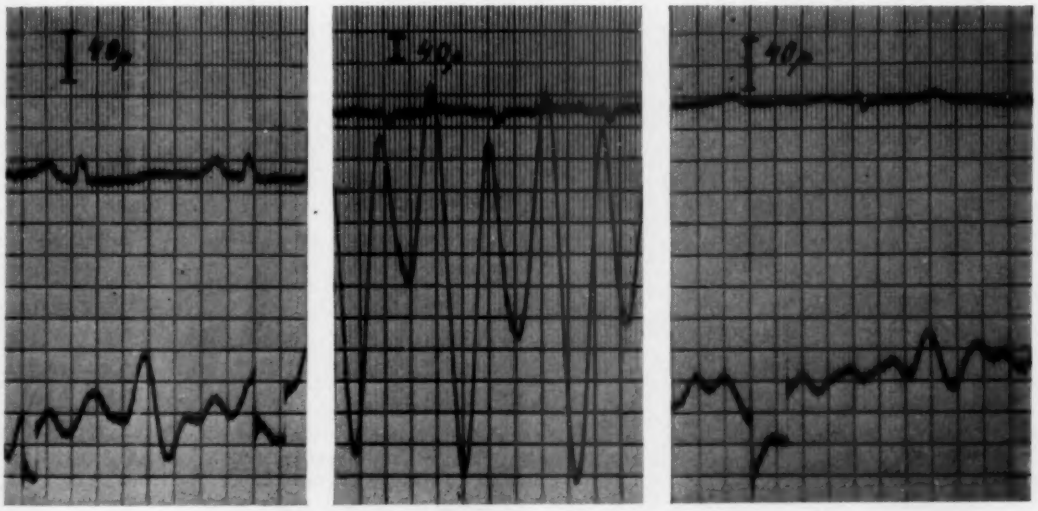
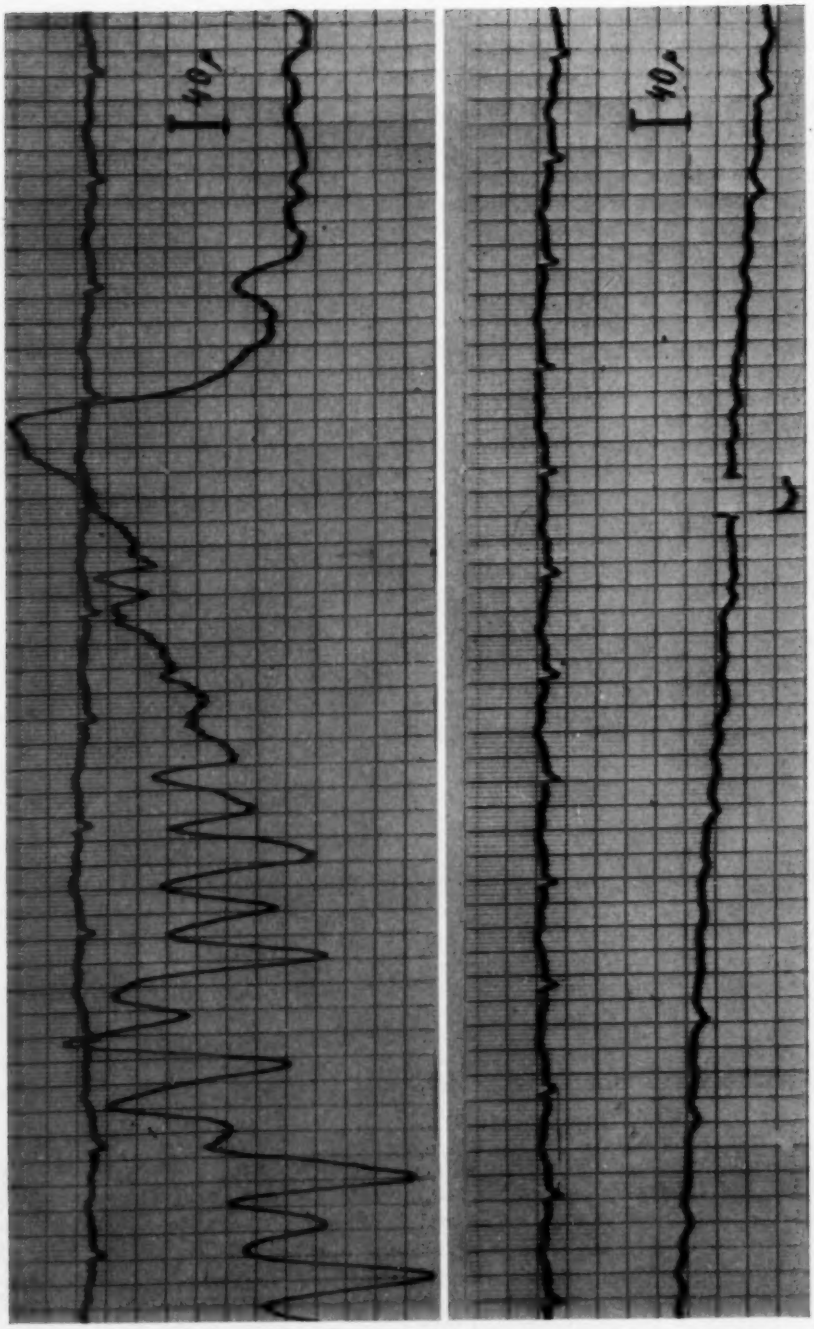


Fig. 5.—E.P., displacement ballistogram taken with respiration suspended in inspiratory position. The height of the columns correspond to 40μ displacement of the cross bar. The tracing to the left was obtained before the occurrence of flush; that in the middle, three minutes later during Stage 2 of a severe flush, and that to the right at the end of Stage 3. The ballistographic waves are deformed in Stage 2, owing to tachycardia. A more normal wave pattern with high amplitudes was obtained in this stage when tachycardia was less pronounced.

and S.H. sometimes felt dizzy and prostrated and vision was blurred. Indirect determination of the arterial blood pressure was often difficult owing to the decrease in the strength of the arterial sounds, but the systolic pressure seemed to persist unaltered. Sometimes the diastolic pressure also persisted unchanged, but sometimes it rose markedly, and then the previously high pulse pressure rapidly decreased. All of these changes were most marked when the cyanosis was sudden, intense, and widespread. Then the amplitudes of the heart contractions and of the systolic ballistographic waves also decreased fairly abruptly (Fig. 6,*A*). Teleradiographic studies showed an increase in the heart volume of S.H. and V.M. by at least 100 c.c. in Stage 2 and Stage 3 (Figs. 8,*A* and *B* and 9,*A* and *B*). The increase exceeds the calculated errors of the method[38] and was found to occur both in ventricular systole and diastole[39] in V.M. The pattern of the respiratory undulations in the ballistograms changed from that of tachypnea and hyperpnea in Stage 2 to that of bradypnea and hypopnea in Stage 3 (Fig. 6,*B*).



A. B.

Fig. 6.—E.P., displacement ballistograms taken during respiration. The upper tracing shows the sudden diminution of the ballistic waves at the end of Stage 2. Below: a section of a tracing from Stage 3. It shows extreme hypokinemia and bradypnea, but the heart rate is still rapid. Heart rate: 136 per minute, respiratory rate: 6 per minute.

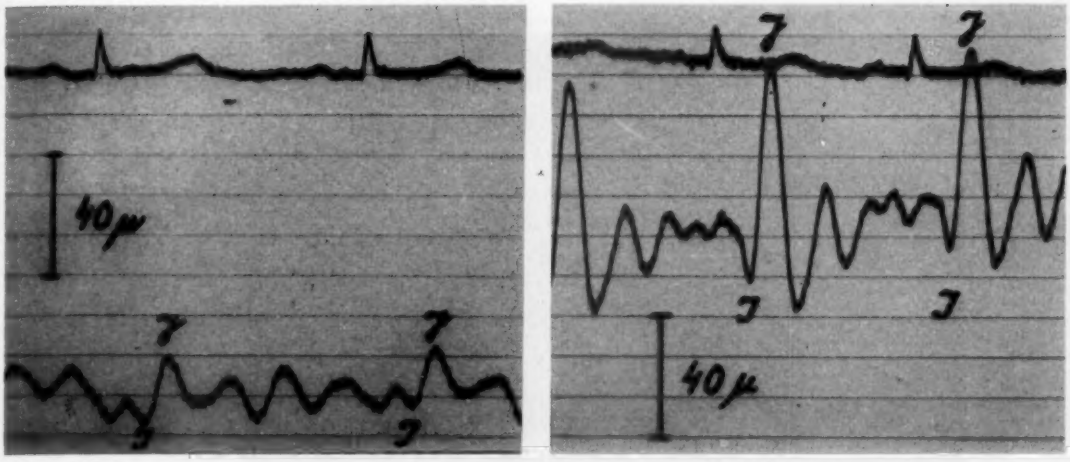
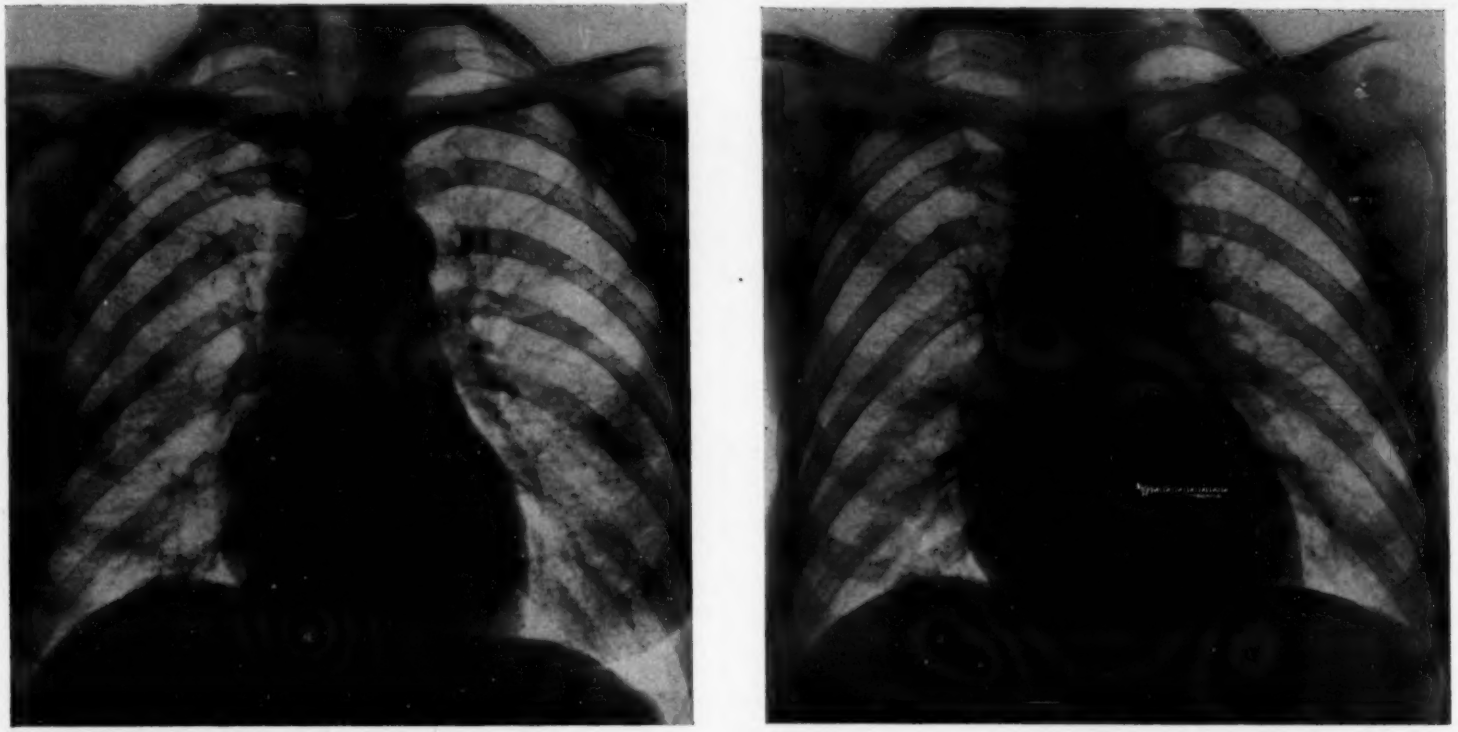


Fig. 7.—S.H., February, 1953, displacement ballistograms taken with respiration suspended in inspiratory position. The left tracing shows small and slightly abnormal waves during a flush-free interval. The right tracing shows moderate hyperkinemia with a normal wave pattern during Stage 2 of a generalized flush.

Stage 3 (*Table III*).—This stage was characterized by patchy or mottled cyanosis. It lasted from one to several minutes. It seems to occur only late in the disease. When cyanosis was severe, the heart sounds and murmurs were faint or inaudible (Fig. 3,*B*). The radial pulse was weak and almost nonpalpable, but the radial artery felt distended. The systolic blood pressure—as long as it could be determined indirectly—was practically the same as during Stage 2. On auscultation one had the impression of a pronounced drop, but on palpation it was often possible to feel the pulse wave go through at about the same pressure level as during Stage 2. The diastolic pressure, which was most often elevated at the onset of cyanosis, soon became immeasurable. On the whole the blood pressure variations were less regular and pronounced than the rest of the observations, and when they occurred, it was mostly in abrupt and intense flushes and cyanotic spells. In the cyanotic stage the heart contractions were fairly small and the ballistographic I, J, and K waves small and rounded (Fig. 6,*B*).

TABLE III. CIRCULATORY PATTERN DURING FLUSH, STAGE 3, FOUND IN E.B., S.H., AND H.B. (V.M. SHOWED NO CYANOSIS)

	FINDINGS	TENTATIVE INTERPRETATION
The skin	Predominantly cold and cyanotic	Contracted precapillary arteries and wide capillaries in the skin. High local vascular resistances. Pooling in the cutaneous capillaries
The pulse	Weak or not palpable. Distended arteries	Small stroke volumes. Low cardiac output. High general vascular resistance. Slight pooling in the systemic arteries
Blood pressure	High systolic pressure. Very low pulse pressure	
Auscultation and phonocardiography	Weak sounds and murmurs	
Ballistography	Low amplitudes	



A. *B.*

Fig. 8.—S.H., April, 1954, teleroentgenograms, frontal planes. The left film was taken just before a moderate flush; that to the right some 60 seconds later, during a moderate flush, Stage 2, about 30 seconds after the beginning of the flush. The heart volume increased from 460 to 560 c.c. Lateral films (not reproduced) showed bulging of the right ventricle in this stage.

A. *B.*

Fig. 9.—V.M., teleroentgenograms, frontal planes, exposure 0.012 second. The left film was taken when she had no flush. The right one a few minutes later during Stage 2 of a moderate flush. The increase in volume (from 710 to 840 c.c.) is obvious. Arrow indicates moment of exposure in cardiac cycle.

COMMENTS ON THE RESULTS

The poor general condition of the patients would not permit all examinations to be made during every stage of flush in each patient. Also, the nature of the examination methods usually precluded simultaneous study of more than two or three variables. Also, not all the flushes were "classical" enough to permit study stage by stage. They were frequently weak and incomplete, or the cutaneous phenomenon was confined to a small area, mostly of the face, and the profound hemodynamic alterations were then also weak. In addition, when the disease was advanced, and the tendency to flush very strong, as in E. P., a state of almost continuous flushing sometimes occurred, in which different areas were seen to flush independently of each other. Each of the local flushes, then, developed at an independent rate, and when they followed each other in fairly quick succession, a many-colored picture was seen, in which it was impossible to decide which stage was dominant, or to compare the general hemodynamic conditions with the components of the cutaneous vasomotor phenomenon. On such occasions, however, the general hemodynamic conditions did not differ much from those found in the intervals between major flushes. This suggested that hemodynamic influences from areas with different colors counteracted each other. If confusion is to be avoided, any statements about central hemodynamic conditions during flush must obviously be made in relation to the stage and severity of the flush. A fair number of "classical" flushes were studied in each patient, and in these, the differences in severity of the reactions were found to vary with the severity and character of the cutaneous flushes. This seems to be true also for the blood pressure reactions.

Strong variations of the ballistographic amplitudes from one part to another of one and the same tracing suggest altered ventricular expulsion, when the patient has not been influenced from without, and the recording technique and apparatus have been unchanged. This is still more probable when the same type of variations is repeatedly found in many flushes and in different patients. Such variations have in this laboratory been observed solely in patients with carcinoids and flush, but may be compared with the monophasically increased ballistographic amplitudes during a pressor attack in a patient with pheochromocytoma, reported by Craig and Schilling.[40] It is debatable if the ballistographic amplitudes are directly proportional to the cardiac output,[41] but it seems certain that such strong alterations of the wave amplitudes in displacement ballistograms can only be caused by output changes. Ballistocardiography also is the only method which continuously gives information about changes in cardiac output without strain or discomfort for the patient. It has been found excellently suited for functional studies in these patients.

With the exception of S. H., cardiac catheterization was not considered justified, because it could not be expected to yield information that might be useful in the treatment of E. P., H. B., or V. M. Therefore no direct recordings were made of the pulmonary circulation. The pressure tracings obtained in S. H. will be included in a separate paper concerning the late development of pulmonary stenosis and tricuspid regurgitation in S. H.[42]

Some of the examination results, particularly the strong gallop sounds, the radiographic and ballistographic findings, were interesting enough to merit

detailed analysis, but suffice it here to suggest one possible interpretation of what happened during the various stages of flush before the occurrence of advanced cardiac changes. Severe valvular lesions probably would have modified the hemodynamic picture.

The flushes have been described stage by stage in this presentation. Chart 1 has been made up from results obtained during several flushes in E. P., and is considered to represent "an average flush" in this patient in August, 1953. It was constructed in the hope that it will give a more vivid impression of the succession of hemodynamic changes during flush.

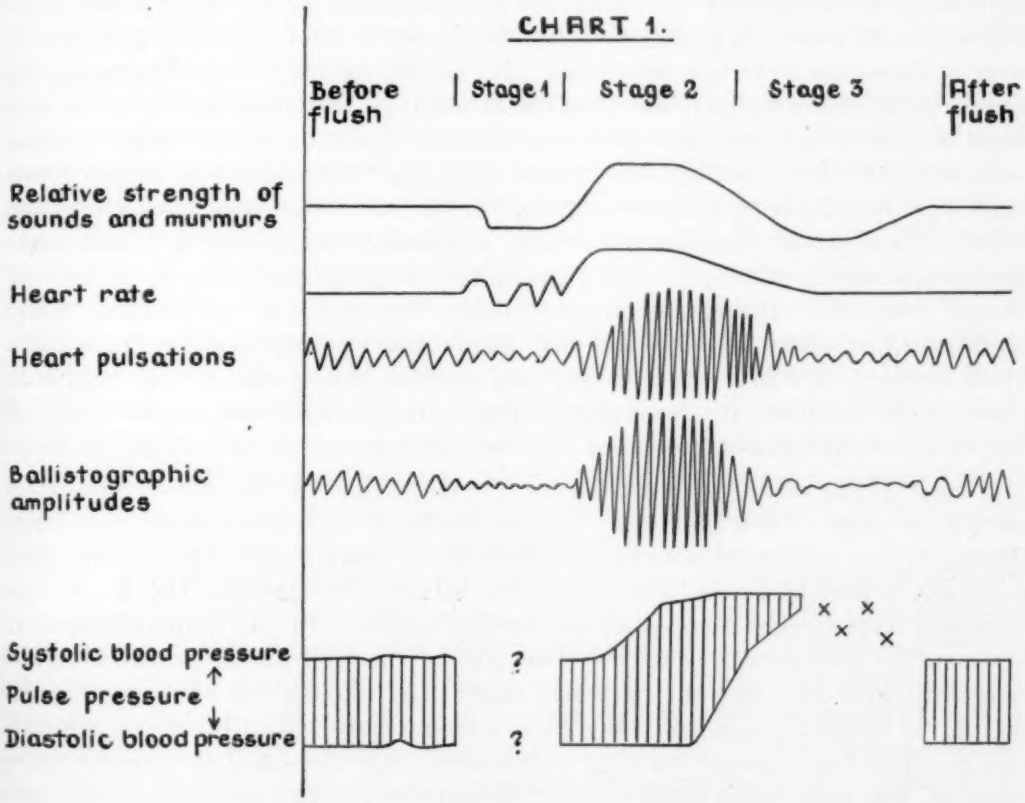


Chart 1.—Graphical demonstration of some variables during "a generalized flush" in S.H. *x* denotes palpatory pressures obtained when auscultatory determination of blood pressures was impossible. The truly enormous intensity of the changes registered readily explains the palpitations and other discomforts of the patient, and makes probable that the changes put a severe strain on the endocardium and eventually cause endocardial sclerosis.

INTERPRETATION OF THE RESULTS

The changes in the color and temperature of the skin were obviously due to local changes in the vascular contraction and rate of flow in the minute cutaneous vessels. At an emergency laparotomy of H. B., it was observed that, during cutaneous flushes, the same type of shifting discoloration occurred in the intestine,

mesentery, and parietal peritoneum, and that the induction of anesthesia was accompanied by severe flushing. That the vessels of the ocular fundi are also sometimes involved by the flush is known.[1]

Stage 1 (*Table I*).—The capillaries and precapillary arteries of the skin dilated progressively. This was closely followed by a decrease in stroke volume and cardiac output (decreased heart sounds and murmurs, heart contractions and ballistic amplitudes, but little changed heart rate). It seems likely that the decrease in output was due at least partly to a transient decrease of the venous return, due in its turn to retarded drainage of the small cutaneous vessels during their successive dilatation. The studies do not indicate whether an instantaneous increase in the pulmonary vascular resistance explained a part of the decrease in output, as the present patients had no bronchoconstriction, and the pulmonary arterial pressures were not measured. K. G., an earlier patient, however, had severe bronchoconstriction, manifest as attacks of bronchial asthma, in this stage of flush, which may have indicated elevated pulmonary pressure and, then, increased pulmonary vascular resistance. Also, too few blood pressure determinations were made during the first stage to permit valid conclusions regarding the order of the systemic vascular resistance. The pressures recorded were not, however, impressively changed. The density of the peripheral lung fields did not change noticeably during any stage of flush, but this does not exclude some changes in the pulmonary blood volume. A successive emptying of the pulmonary blood depot in this brief stage might help to explain why the systolic systemic pressure did not decrease profoundly. The state of contraction or dilatation of the vessels in the skeletal muscles was not determined in any stage of flush.

Stage 2 (*Table II*).—In this stage the dilatation of the small cutaneous vessels was more or less constant. During this time the stroke volume was large (palpitations, loud heart sounds and murmurs, vigorous and large heart contractions, high and peaked ballistographic waves). Frequently the heart rate increased with further increase of the cardiac output. In one patient, however, bradycardia sometimes occurred. The normal diastolic blood pressure simultaneously with high systolic pressure, heart rate, and output showed that the peripheral resistance was low, since there were no signs indicating aortic regurgitation. The high cardiac output, which sometimes persisted for one or more minutes, also indicated a rapid circulation and made a high elevation of the pulmonary resistance improbable. Apart from the dilatation of the small peripheral vessels, no signs were seen of a major redistribution of blood from one part of the vascular bed to another.

During the transition to Stage 3 a more or less rapid shift to the hemodynamic characteristics of this stage could be followed.

Stage 3 (*Table III*).—This stage, the cyanotic stage, was dominated by contraction of the precapillary arteries in the skin with dilatation of the following capillaries (cold and cyanotic areas), suggesting an increase in the peripheral resistance in the skin and, probably, some pooling of blood in the cutaneous capillaries. In agreement with this, the total peripheral resistance was also increased (high diastolic blood pressure, but low pulse pressure; and distended arteries in the presence of a low output). The stroke volume and cardiac

output were low (faint or inaudible sounds and murmurs, small heart contractions and ballistographic amplitudes, a weak peripheral pulse, probably normal systolic pressure simultaneously with a low pulse pressure, and slightly increased or normal heart rate). There were no electrocardiographic changes indicating coronary insufficiency and no anginal pain in either stage.

DISCUSSION

It was obvious that the cutaneous vasomotor phenomena during the phenomenal flush were only one part of a profound and often intense hemodynamic reaction. Such a reaction might occur even in the absence of color changes in the skin, because in V. M. the peripheral pulse sometimes changed character, and/or became impalpable for one or several minutes, without any accompanying discoloration of the skin or discomfort.

It was impressive that all four patients had the same sequence of hemodynamic changes during major flushes, but they all had a fairly advanced type of flushing, and it is not certain, perhaps not even probable, that all patients with metastatic carcinoid tumors and flushing react according to the pattern found in three of our four patients (V. M. had no cyanotic stage). This is suggested by the somewhat differing type of flush reported by some observers. Also, Daugherty and associates[21] found decreased blood pressure during flush in their patient. It may, however, be fairly common, as Snow and associates[20] in two of their patients noted a slight increase of the systolic blood pressure and pulse pressure in what seems to correspond to the second stage of flush. A third patient (their Case 2) repeatedly became severely cyanotic and weak, and at the same time her pulse became impalpable for long periods. This seems to correspond to the conditions during Stage 3 in this series, but the reactions of their patient were still more violent and resulted in a manifest "circulatory collapse."

In the four patients studied here, the variations of the vascular tonus, the distribution of blood, the stroke volume, and the heart rate apparently balanced each other and thereby prevented a circulatory disaster. It is possible, however, that the extreme weakness and blurred vision during the cyanotic stage in E. P. and S. H. were caused by cerebral hypoxia due to slow cerebral circulation. This explanation is suggested by the retinal cyanosis in K. G.[1] and, during collapse, in Case 2 in the series of Snow and associates, and cerebral hypoxia might be the direct cause of the tendency to fainting during cyanotic attacks in some of the patients with carcinoidosis.

The nature of the examination methods used, and the subjective element in the determination of the onset of the various stages do not permit any definite conclusions as to the primary cause of the hemodynamic changes, but the studies indicate the direction and magnitude of the shift of the various variables. The variation in cardiac output was chiefly brought about by changes in stroke volume and only to a lesser extent by shifts in the heart rate. The increase in stroke volume in Stage 2 was sometimes large. In this stage dilatation of the heart, most likely of the right half of the heart, was found in two of the patients, and intracardiac pressure pulse tracings from one of them at a later date[42] showed transient tricuspid regurgitation in Stage 2. This implies repeated stretching of the struc-

tures in the heart during the flushes, repeated many times daily for a long time, and might help to explain the late development of endocardial sclerotic lesions in some of these patients. According to this view, the endocardial sclerosis is caused by the released specific endogenous substances indirectly and by the mechanical action of the general hemodynamic changes rather than by direct action on the endocardium from the liberated substances. This is further discussed in another paper concerning the structural heart lesions.[43]

It seems natural to assume that the flushes are initiated by released 5-hydroxytryptamine, and this assumption is strongly supported by the investigation by Roddie and associates,[44] in which short-term infusion of 5-hydroxytryptamine into the brachial artery produced flushing of the forearm and hand followed by cyanosis of the hand in healthy volunteers. It is, however, curious that peripheral vasodilatation is so pronounced. This may be due to regulatory mechanisms as yet insufficiently understood. It must be remembered that in the patients the released substance has to pass the pulmonary circuit before it reaches the central nervous system or the cutaneous vessels, and it is known that 5-hydroxytryptamine increases the pulmonary vascular resistance and the pressure in the pulmonary artery in animal experiments. Also, 5-hydroxytryptamine may liberate histamine,[45] which might explain the vascular dilatation,[44] and also the local edema, the spells of headache, and the favorable effect of antihistaminics in some of the patients. Waldenström and associates[46] have found a high histamine content in blood and urine from patients with carcinoidosis, which lends some support to this explanation, but Snow and associates found no histamine in their cases.[20]

It would have been interesting to study the effect of 5-hydroxytryptamine on the circulatory system in these patients. Owing to the alarming severity of some of the spontaneous hemodynamic reactions in the patients and our lack of knowledge of the risks involved, it was decided to postpone any administration until more is known about any possible risks.

Comparisons of the results reported here with the effect of 5-hydroxytryptamine on healthy volunteers or on hypertensive subjects[47] must be made with caution owing to a possible adaptation of the organism to the principle liberated in excessively large quantities from the tumor, a possibility supported by the known tachyphylaxis of animals to the effect of 5-hydroxytryptamine on the blood pressure,[32] and also by the slow adaptation of rats to repeated administration of large doses of the substance.[48] It is also impossible to administer 5-hydroxytryptamine in single injections or as short-term infusion to man in quantities comparable with those found circulating in our patients.[29]

Comparison of the results in animal experiments with clinical observations must also be made with caution, because, besides the difference in response in different species, there also exists individual variations within the species, and variations due to the general experimental conditions, the dosage, and the mode of administration. If such comparisons should be made, it seems preferable to compare the clinical findings with those found in dogs after the administration of 5-hydroxytryptamine in large doses. The studies by MacCanon and Horvath[49] on a great number of dogs, in which direct registration was made of the systemic and

pulmonic circulatory response and the respiratory reactions, may be mentioned in this connection. They found, constantly, after five seconds a simultaneous elevation of the pulmonic and the femoral arterial blood pressure, lasting a few minutes. The pulmonary and systemic vascular resistance increased during the first few seconds of the pressor phase. A few seconds later, the cardiac output and the vascular resistance in the systemic and also in the pulmonary circulation increased and remained elevated until the end of the pressor phase. Usually, a brief arrhythmia followed by bradycardia was found during the pressor phase. Constantly, a short initial period of hyperpnea was followed by a more protracted period of reduced respiratory activity. Shifts in the respiratory records suggested bronchoconstruction.

It is obvious that many similarities exist between the circulatory and respiratory findings in this series and those reported by MacCanon and Horvath, even though the results are not identical.

SUMMARY AND CONCLUSIONS

Four patients with metastatic carcinoid tumors were examined during flush episodes.

Initially, the cardiac sounds, murmurs, contractions, and ballistocardiographic waves diminished.

Next, when the cutaneous vasodilatation was complete, the cardiac sounds, murmurs, contractions, and ballistographic waves increased considerably and tachycardia was common, but, sometimes, slight bradycardia occurred. In this stage, the systolic blood pressure frequently rose, and hyperpnea and tachypnea were observed.

Finally, when the reddening was succeeded by pronounced cyanosis, the cardiac sounds, murmurs, contractions, and ballistic amplitudes again decreased, the diastolic brachial pressure sometimes rose markedly, and the radial pulse became impalpable. Hypopnea and bradypnea were sometimes noted. The changes disappeared with the regression of the cyanosis.

It is concluded that hypokinemic and hyperkinemic stages alternate with different phases of the cutaneous vasomotor disturbance and probably place an increased strain on the heart. This might help to explain the development of sclerotic endocardial lesions in these patients.

SUMMARIO IN INTERLINGUA

Quatro patientes con metastatic tumores carcinoide esseva examinate durante episodios de rubor.

Initialmente, le cardiac sonos, murmures, contractiones, e le undas ballistocardiographic se reduceva.

Postea, quando le vasodilatation esseva complete, le cardiac sonos, murmures, contractiones, e le undas ballistocardiographic se augmentava considerabilemente. Tachycardia esseva commun ben que il habeva a vices leve grados de bradycardia. In iste stadio, le pression de sanguine systolic accresceva frequentemente, e hyperpnea e tachypnea esseva observate.

Finalmente, quando le rubor esseva sequite per pronunciate grados de cyanosis, le cardiac sonos, murmures, contractiones, e le amplitudes ballistic se reduceva de novo, le diastolic pression brachial se augmentava a vices marcatemente, e le pulso radial deveniva impalpabile. Hypopnea e bradypnea esseva notate a vices. Le alterationes dispareva con le regression del cyanosis.

Es deducite le conclusion que stadios hypocinemic e hypercinemic occurre in alternation insimul con differente phases del cutanee disturbation vasomotor e impone possibilemente un effortio augmentate super le corde. Isto contribue forsan al explication del disveloppamento de sclerotic lesiones endocardial in iste patientes.

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Clinical Reports

ABERRANT VENTRICULAR CONDUCTION SIMULATING PAROXYSMAL VENTRICULAR TACHYCARDIA DURING QUINIDINE THERAPY

MARIANO M. ALIMURUNG, M.D.,* AND MANUEL CHUA CHIACO, M.D.**

MANILA, PHILIPPINES

PRECISE diagnosis in cardiac arrhythmias is a task frequently difficult to accomplish, even with the aid of the electrocardiogram. Prognostication and intelligent management can be attained only through a precise identification of the existing arrhythmia. Easily mistaken for ventricular tachycardia is aberrant ventricular conduction. Such a differentiation is of clinical importance because, as Langendorff[1] states, whereas digitalis is best avoided in ventricular tachycardia, this drug is often the treatment of choice for supraventricular tachycardia.

The term "aberration" has been defined by Sir Thomas Lewis[2] as the "abnormal distribution of a supraventricular impulse in the ventricle" due to "defects in conduction through some of the chief Purkinje strands." Since then, several excellent articles on the subject have been written.[3-6] Still, this arrhythmia continues to offer difficulties in clinical practice and is not as frequently recognized as it probably occurs.

We are reporting a case wherein aberrant ventricular conduction at a rapid heart rate developed and was apparently related to quinidine therapy. In such an instance, prompt recognition of the true nature of the arrhythmia assumes greater clinical significance because, like the case of digitalis, quinidine is of therapeutic value if the arrhythmia is a true ventricular tachycardia. On the other hand, aberrant ventricular conduction itself would be an indication of quinidine intolerance or toxicity.

CASE REPORT

J. C. H., 50-year-old married Chinese businessman, came under our care on Nov. 9, 1952, for cardiac evaluation. The history revealed that he underwent a subtotal thyroidectomy in 1930 for toxic goiter. The latter was manifested by palpitation, nervousness, mild exophthalmos,

*Associate Professor of Medicine and Acting Chief of Cardiovascular Section, University of Santo Tomas, College of Medicine; and Chief of Clinics, Santo Tomas University Hospital, Manila.

**Cardiologist and Medical Director, Chinese General Hospital, Manila.

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and moderate enlargement of the thyroid gland. Since 1950 he had been known as a mild hypertensive with an average blood pressure of 160/100 mm. Hg.

He had nine children. His father died of pulmonary tuberculosis. One brother died of a liver new growth, and one sister had bronchial asthma.

In that first examination the only abnormality noted was the occurrence of auricular premature beats (Fig. 1).

From Feb. 19 to March 21, 1953, he was hospitalized for an acute infectious hepatitis with fever, jaundice, nausea, vomiting, anorexia, headache, and general weakness. During the early part of that illness, he complained of periods of palpitation. It was then observed that his radial pulse was irregular. The electrocardiogram (Fig. 2,*A*) revealed atrial fibrillation with an average ventricular rate of 140 per minute. Quinidine reverted the fibrillation so that at the time of discharge from the hospital, he had a normal sinus rhythm with a rate of 96 per minute (Fig. 2,*B*).

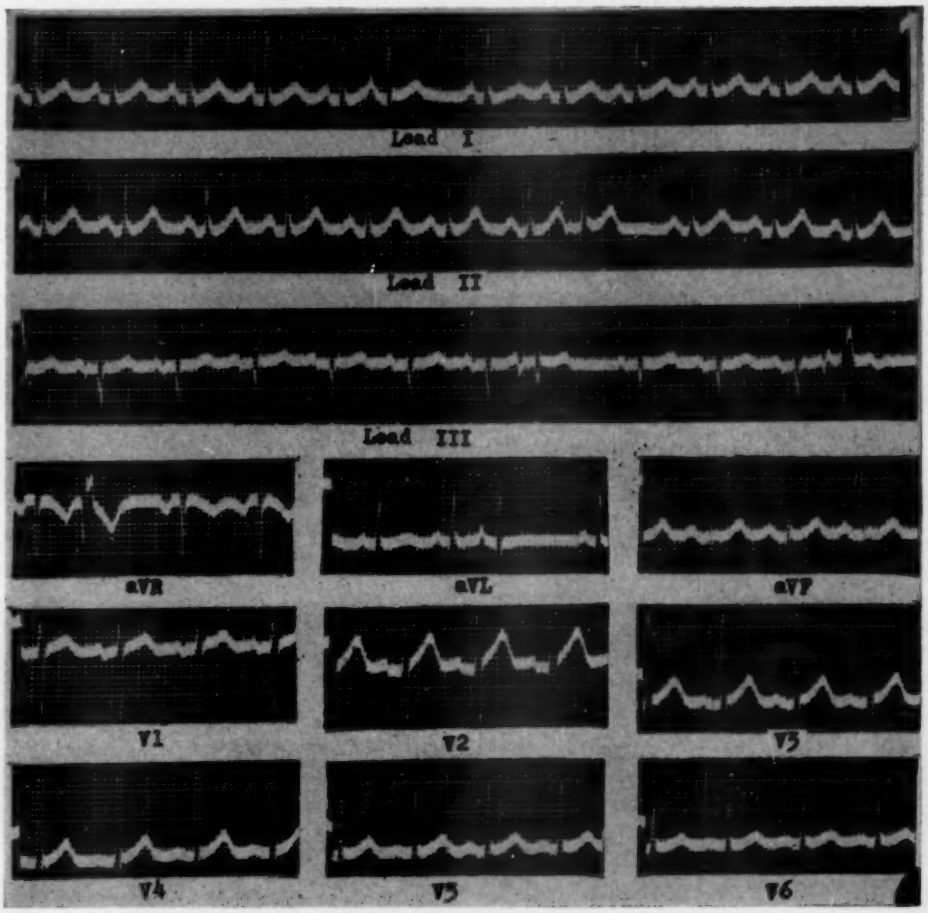

Fig. 1.—Initial electrocardiogram showing minimal sinus tachycardia and atrial premature beats.

About five months later, atrial fibrillation reappeared with an average ventricular rate of 110 per minute (Fig. 2,*C*). Quinidine was again instituted. After receiving a total of 32 tablets of 0.20 Gm. each of quinidine sulfate in two and one-half days, he developed paroxysms of rapid heart action with a ventricular rate reaching 170 per minute. The electrocardiogram (Fig. 3) disclosed paroxysms of rapid ventricular rate with bizarre and widened ventricular complexes. He then complained of rapid and pounding heart beats, nervousness, nausea and vomiting, loose bowel movements, abdominal cramps, and general malaise. At first the electrocardiogram was thought to be paroxysmal ventricular tachycardia. On the suspicion that this arrhythmia could be due to quinidine sensitivity or toxicity, the drug was discontinued.

Pronestyl was then given by intravenous drip. He received a total of 1,000 mg. in about twelve hours. Finally this was also stopped and he was then given digitoxin. Gradually the arrhythmia subsided and the cardiac mechanism returned to atrial fibrillation. At the time of discharge, July 18, 1953, he was receiving a maintenance dose of digitoxin, 0.2 mg. a day.

To date, he still shows atrial fibrillation (Fig. 4), but he is apparently tolerating this arrhythmia fairly well. With digitoxin his average ventricular rate is kept below 100 per minute. He has not received quinidine again nor has he had any more paroxysms of tachycardia as described above.

The rest of the cardiac examination has always been unremarkable. No murmur has ever been heard nor has there ever been any evidence of cardiac enlargement even by x-ray. His physical tolerance remains good.

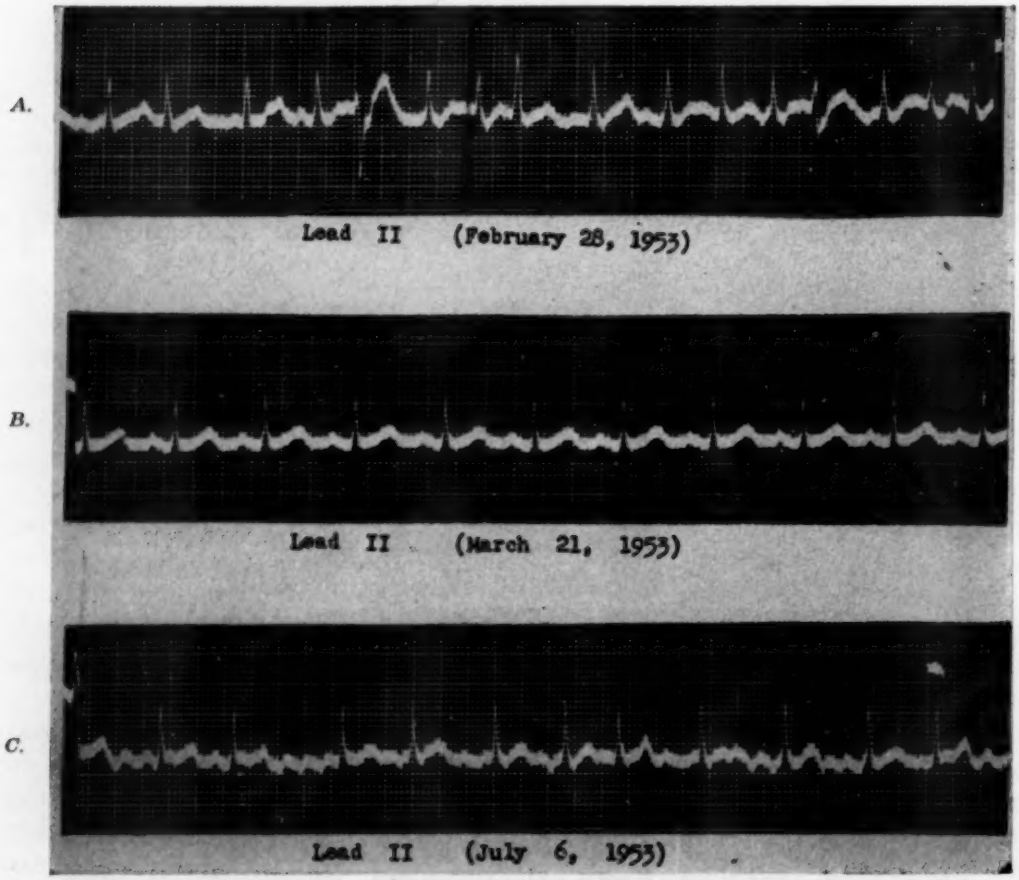

Fig. 2.—Lead II electrocardiograms. On Feb. 28, 1953, there was atrial fibrillation with some QRS complexes showing bizarre configuration. Normal sinus rhythm is shown on March 21, following quinidine. Lower tracing, on March 6, shows reappearance of atrial fibrillation.

DISCUSSION

Briefly, therefore, there was initially a basic sinus rhythm with auricular premature beats. Then atrial fibrillation set in, which responded well to quinidine by reverting readily to sinus rhythm. Atrial fibrillation reappeared and subsequent quinidine therapy with a larger dose provoked paroxysms of rapid heart action with bizarre and widened ventricular complexes mistaken for ven-

tricular tachycardia. At the same time he developed a number of constitutional manifestations. Quinidine was discontinued, digitoxin was given instead, and the bizarre QRS complexes disappeared. Atrial fibrillation recurred and has persisted since then, the ventricular rate being controlled by maintenance digitoxin.

Of special interest is the appearance of paroxysms of rapidly occurring bizarre and widened QRS complexes. As has happened in similar instances in the medical literature, this arrhythmia was initially interpreted as paroxysmal ventricular tachycardia. Cases of ventricular tachycardia occurring during quinidine therapy have been reported.[7,8] On the other hand, it is also recognized that quinidine is an effective treatment for ventricular tachycardia.

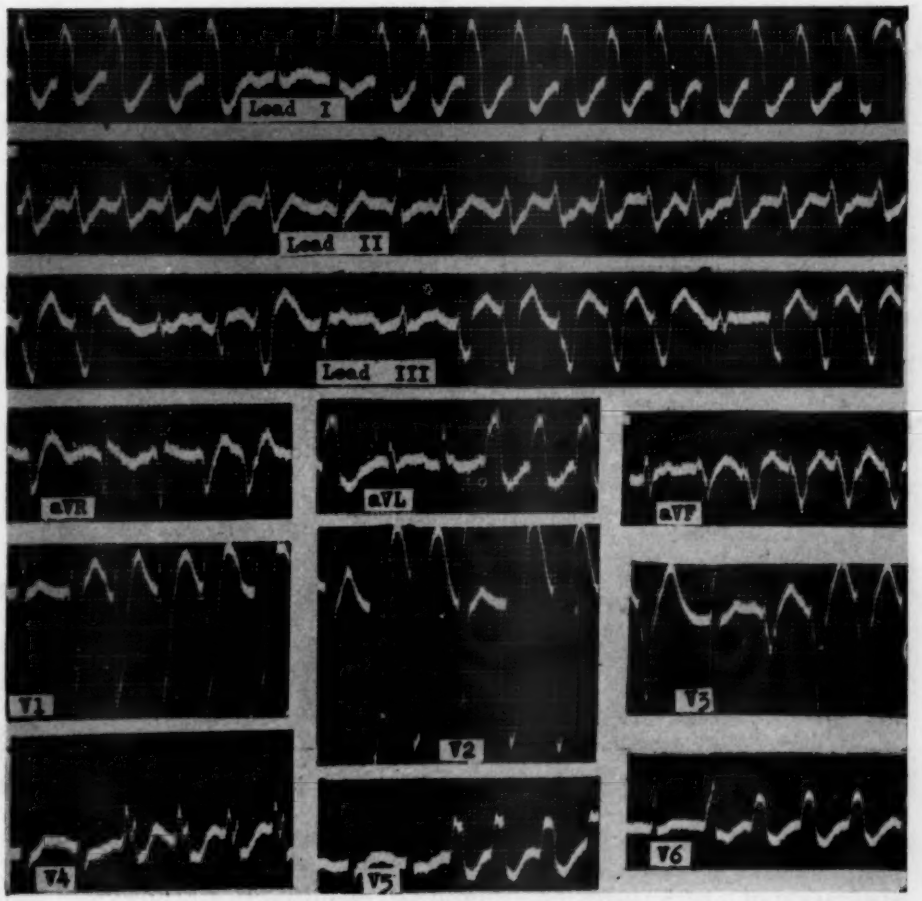

Fig. 3.—Electrocardiogram showing the paroxysms of bizarre and widened QRS, initially considered as paroxysmal ventricular tachycardia, but on closer study were instances of aberrant ventricular conduction (discussion in text).

More detailed scrutiny of the electrocardiogram disclosed that one was dealing here with a supraventricular tachycardia with aberrant ventricular conduction. The differential diagnosis between aberrant ventricular conduction with a rapid ventricular rate and ventricular tachycardia is often difficult, if not impossible.[9] The same difficulty has been found in reports of ventricular tachy-

cardia which are truly supraventricular tachycardia associated with the W-P-W syndrome of anomalous atrioventricular conduction.[10] Barker, Johnston, and Wilson[11] reported a patient with sinus tachycardia who developed an electrocardiographic picture of right bundle branch block on two occasions after the administration of quinidine. Similar cases of aberrant ventricular conduction during atrial fibrillation and quinidine therapy have been reported by Miller[3] and by Gouaux and Ashman.[4]

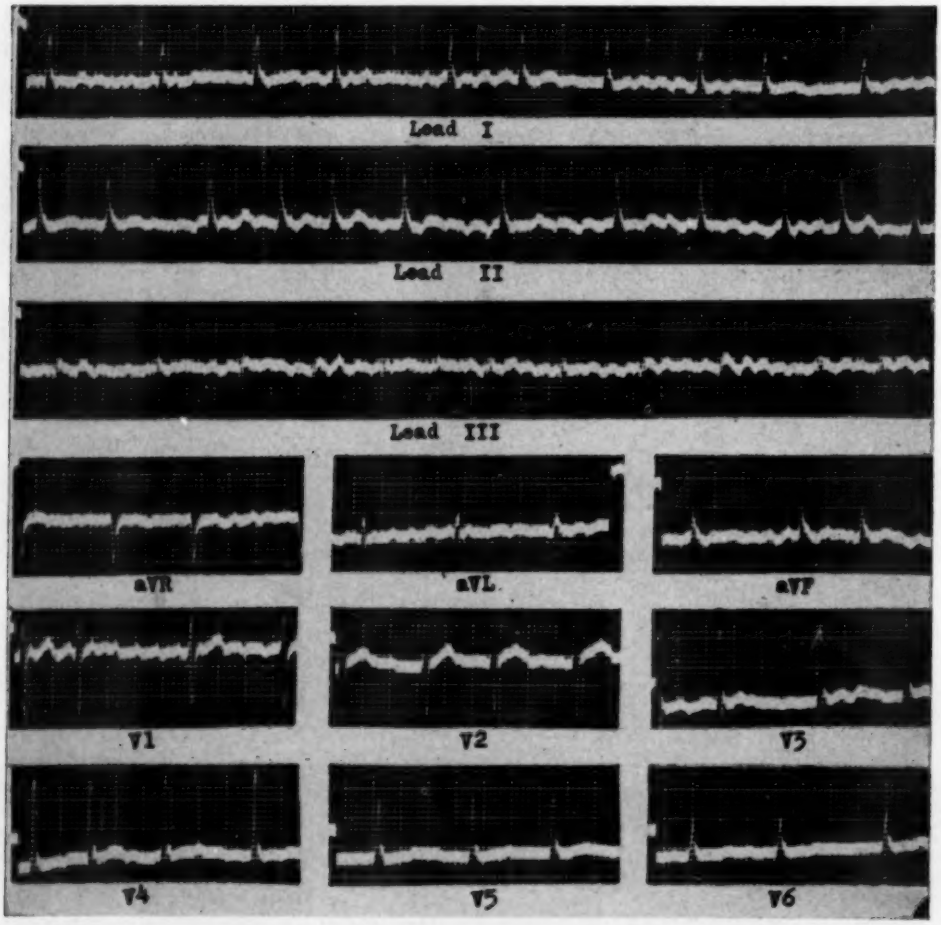

Fig. 4.—Atrial fibrillation shown after quinidine was stopped.

Aberration of a supraventricular impulse[12] resulting in a bizarre and widened ventricular complex occurs when the impulse appears early in diastole of the preceding beat before recovery has been completed in all parts of the conducting tissues. The experimental studies of Lewis and Master[13] on atrioventricular conduction and of Scherf[14] on intraventricular conduction demonstrated that the recovery curve for a given cycle is influenced by the preceding cycle. The sooner a supraventricular impulse arrives at the intraventricular conducting tissue, the more likely is it to meet either one bundle branch or a main strand of Purkinje fibers refractory. Functional fatigue blocks giving rise to critical rates of ven-

tricular conduction have been pointed out by Vessell and Kraemer.[15] Thus, in a case of two premature systoles with identical coupling but with varying duration of the preceding cycle, the one which follows the longer cycle is more prone to exhibit aberrant ventricular conduction, since the duration of the refractory period is shorter after a shorter preceding cycle.

An important diagnostic clue in our case is the significant difference in configuration of the initial aberrant QRS in each paroxysm from the normally conducted complex as well as from the succeeding aberrant ones. This initial aberrant complex occurred whenever a short cycle followed a preceding long cycle, so that a short cycle was terminated by a ventricular complex showing a bundle branch block pattern. When this aberration occurred singly, there was no compensatory pause. In the case of a premature ventricular beat, such a pause would be present and would generally be a complete compensatory pause. This lack of postextrasystolic compensatory pause is emphasized by Langendorff[5] and Katz[16] as an important differential point between ventricular ectopic beats and aberrant ventricular conduction of supraventricular impulses. This observation is particularly important when there exists atrial fibrillation, as in the present case, wherein the use of the P wave for differential diagnosis is not feasible.

Greater degree of aberration of the QRS complex occurred when the succeeding cycle was still shorter and thus the supraventricular impulse reached the bundle branch even more refractory. When such cycles continued, a series of aberrant QRS complexes followed until a supraventricular impulse finally arrived late enough in the cycle to permit sufficient recovery of both bundle branches in order that ventricular conduction could be normal again. Such series of rapidly occurring aberrant ventricular complexes are the ones often misinterpreted as paroxysmal ventricular tachycardia.

Finally it must be noted that the basic QRS configuration did not radically change whether the ventricular conduction was aberrant or not. This finding is also in favor of the supraventricular origin of the impulses.

That this arrhythmia occurred during quinidine therapy must be emphasized. While not particularly stressed, this association is found in many similar cases reported in the literature. The accompanying nausea, vomiting, and loose bowel movements give added evidence to the role of quinidine as etiologic agent to the entire syndrome. Disappearance of these manifestations and the arrhythmia, with discontinuation of quinidine, strongly suggests this causal relationship.

Prompt recognition of this arrhythmia and its relationship with quinidine is of practical importance. Diagnostically, it would suggest quinidine intolerance or toxicity. Prognostically, it would not convey the gravity often attached to ventricular tachycardia. Therapeutically, it would indicate discontinuation of quinidine and administration of digitalis.

SUMMARY

A case of aberrant ventricular conduction simulating paroxysmal ventricular tachycardia is reported. This arrhythmia occurred in a 50-year-old man with mild hypertension and atrial fibrillation, while under quinidine therapy.

The etiologic role of quinidine is suggested by: (1) the occurrence of the arrhythmia during quinidine administration; (2) appearance of other clinical manifestations such as nausea, vomiting, and loose bowel movements; and (3) disappearance of both the clinical symptoms and the arrhythmia upon discontinuation of quinidine.

The diagnostic, prognostic, and therapeutic importance of prompt recognition of this arrhythmia is pointed out. The criteria for electrocardiographic diagnosis and the mechanism of production of aberrant ventricular conduction are discussed.

SUMMARIO IN INTERLINGUA

Es reportate un caso de aberrante conduction ventricular, simulante tachycardia ventricular paroxysmal. Iste arrhythmia occurreva in un masculo de 50 annos con leve hypertension e fibrillation atrial durante que ille esseva sub therapia a quinidina.

Le responsabilitate etiologic del quinidina es indicate per le fectos que (1) le arrhythmia occurreva durante le administration de quinidina, (2) altere manifestationes clinic appareva, includente nausea, vomito, e feces relaxate, e (3) tanto le symptomas clinic como etiam le arrhythmia dispareva post le interruption del curso de quinidina.

Es signalate le importantia diagnostic, prognostic, e therapeutic del prompte recognition de iste arrhythmia. Es discutite le criterios del diagnose electrocardiographic e le mechanismo generative de aberrante conduction ventricular.

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COARCTATION OF THE PULMONARY ARTERY

JOHN E. COLES, CAPTAIN, USAF (MC), AND
WELDON J. WALKER, LIEUTENANT COLONEL, MC, USA

FORT SAM HOUSTON, TEX.

SONDERGAARD[1] has recently reported three patients who, at surgery, had a localized constriction at the beginning of both branches of the pulmonary artery. In at least one case this constriction appeared to be associated with an extension of fibrous bands from the ligamentum arteriosum that looped around and constricted both the right and left branches of the pulmonary artery. He designated this condition "coarctation of the pulmonary artery." In each patient there was associated pulmonic stenosis. He suggested that this condition may be relatively common. He encountered these three cases during the three-year period following adoption of the routine of opening the pericardium at surgery to obtain maximum information on all cases of congenital heart disease. He also cited a case by Shumacher and Lurie[2] who reported successful dilatation of a constriction of the origin of the left pulmonary artery by inserting and opening a Kelly clamp.

It is the purpose of this paper to report a patient who, by means of angiocardiographic and cardiac catheterization data, appears to have this form of coarctation of the pulmonary artery. It is of interest that our patient also has pulmonary stenosis.

CASE REPORT

This 26-month-old white female child was born following a normal pregnancy and delivery. Birth weight was 8 pounds, 11 ounces. A cardiac murmur was noted at the time of birth and her color was considered somewhat dusky when she cried, but there had never been marked cyanosis. The child had manifested a poor appetite, decreased exercise tolerance, and poor weight gain since birth. Her weight at 26 months was 23 pounds. There had been no recent cyanosis and there was no clubbing of the extremities. The principal findings were a harsh Grade 4 systolic murmur in the pulmonic area with an associated thrill. The pulmonic second sound was slightly decreased. Cardiac fluoroscopy showed the heart size to be at the upper limits of normal with slight prominence of the main pulmonary artery, and normal to decreased vascularity in the peripheral lung fields. No specific chamber enlargement was demonstrated. The aortic arch was on the left. The electrocardiogram revealed marked right ventricular hypertrophy. Ear oximeter revealed 97 per cent oxygen saturation. A diagnosis of valvular pulmonary stenosis with possible associated interatrial septal defect was made. Cardiac catheterization was attempted on Mar. 29, 1955, through the left and later the right median basilic vein with a number 5 catheter.

From the Cardiovascular Service, Brooke Army Hospital, Fort Sam Houston, Tex.
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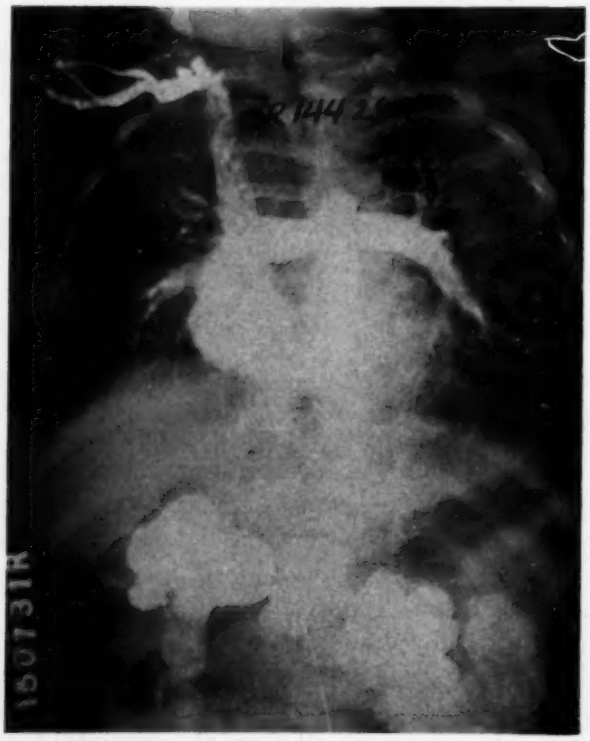

Fig. 1.—Angiocardiogram made one and one-half seconds following the beginning of injection of Urokon. Note the apparent narrowing of the proximal portion of both the right and left pulmonary arteries.

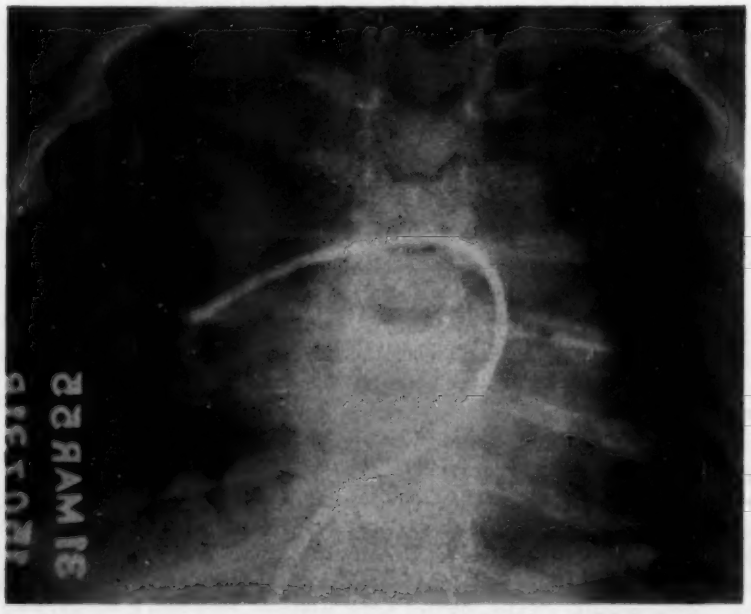

Fig. 2.—Cardiac catheterization via the saphenous route. Catheter tip in right pulmonary artery.

On both occasions severe venospasm developed after the tip of the catheter had reached the region of the right atrium, which prevented manipulation or further advancement of the catheter. However, 11 c.c. of 70 per cent Urokon was rapidly injected into the cannulated vein and films were taken at one-half second intervals (Fig. 1). These revealed a normal sequential filling of the cardiac chambers without early opacification of the aorta. The radiologist, Dr. P. E. Siebert, noted an apparent narrowing of the initial portion of each of the pulmonary arteries and reported, "At the region of the bifurcation of the pulmonary artery, the diameter of the lumen measures approximately 8 mm. on the right and 10 mm. on the left. About 1.5 cm. distal to this point the right pulmonary artery measures 14 mm. and the left 12 mm. The significance of this finding is not known." Two days later cardiac catheterization was repeated through the right saphenous vein. The catheter took a normal course into the right pulmonary artery where the pressure

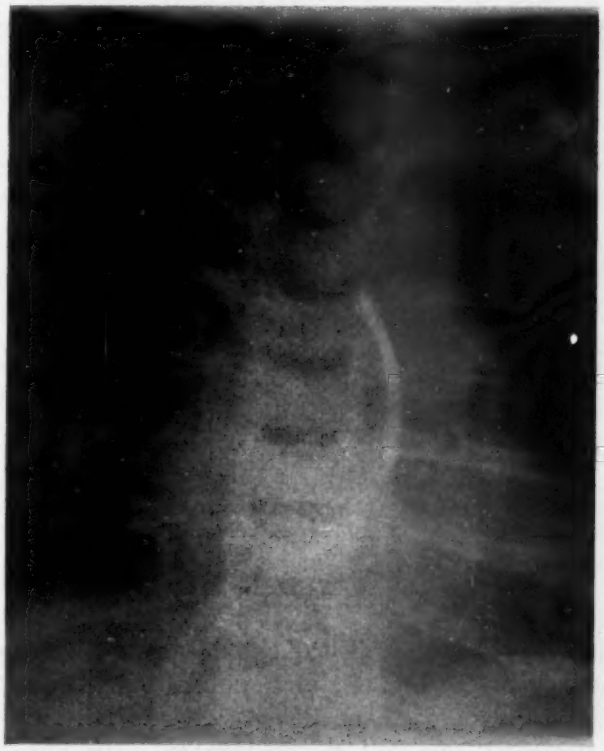

Fig. 3.—Location of catheter tip when intermediate pressure was recorded. Note that the catheter tip is higher than the level of the right pulmonary artery (see Fig. 2). An infundibular chamber could not lie cephalad to the right pulmonary artery.

was 15/5 mm. Hg. On withdrawal of the catheter, with continuous pressure recording, it was noted that the pressure suddenly rose to 50/8 mm. Hg as the tip of the catheter seemed to flip from the right into the main pulmonary artery. At the time this higher pressure was recorded, the tip of the catheter was farther cephalad than when it was in the right pulmonary artery (Figs. 2, 3, and 4). This would seem to rule out the possibility of the tip being in an infundibular chamber. On further withdrawal of the catheter, there was again a sudden change of pressure as the tip of the catheter traversed the region of the pulmonary valve, with an increase in the systolic and a reduction of the diastolic pressure. The catheter was again introduced into the right pulmonary artery and the same sequential pressures were again obtained. Radiographic pictures were obtained recording the location of the catheter tip at the time each pressure curve was obtained. Efforts to introduce the catheter into the left pulmonary artery were un-

successful. The catheter was then introduced into the left atrium through a patent foramen ovale. Blood oxygen determinations, however, failed to demonstrate an appreciable shunt through this defect and arterial blood was 96 per cent saturated.

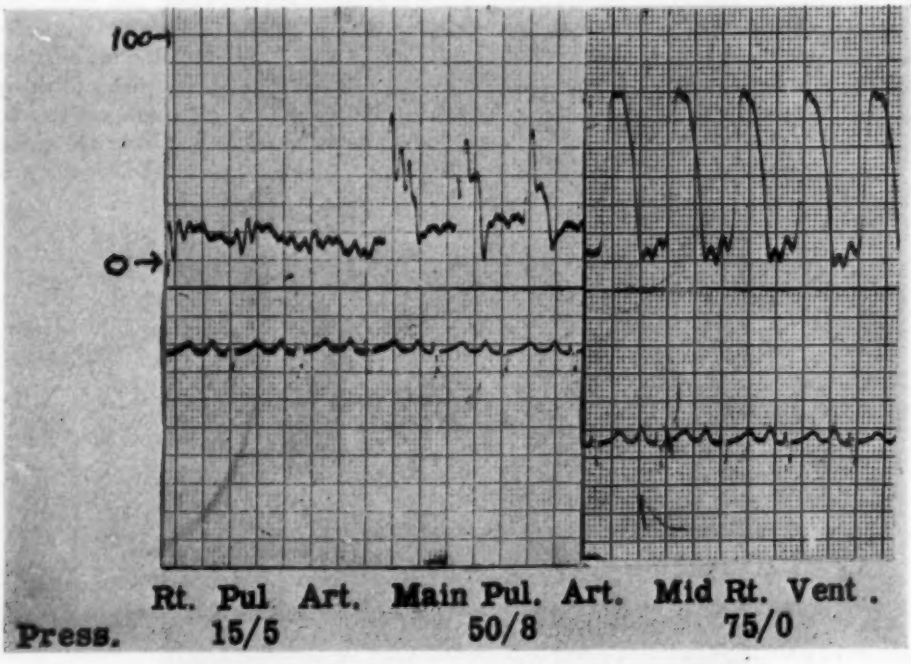

Fig. 4.—Pressure curves on withdrawal of catheter that was free in the right pulmonary artery. Note the sudden change on continuous record as tip flipped from right into main pulmonary artery (location of catheter tip shown in Fig. 3). Note that systolic pressure in the main pulmonary artery is lower and diastolic pressure higher than that recorded from the right ventricle.

DISCUSSION

It seems surprising that Sondergaard[1] should observe three cases of coarctation of the pulmonary artery in the short span of three years, as prior to this time it had not been recognized as a disease entity by pathologists, cardiologists, or cardiac surgeons. In fact the failure to have encountered such an entity has been the chief argument used against the scodaic theory of the etiology of coarctation of the aorta.[3] This theory postulates that coarctation is produced by an extension of tissue from the ductus arteriousus into the aortic wall, which contracts as the ductus undergoes obliteration. It has been argued that since such contraction had not been observed at the pulmonary artery end of the ductus, the hypothesis was untenable.

The catheterization findings of a patient similar to ours was presented by Dr. Hodges of Ann Arbor at a pannel discussion on cardiovascular diseases at the recent meeting of the American Medical Association in Atlantic City.[4] In his patient the cardiac catheter had been successfully introduced into both branches of the pulmonary artery and on withdrawal into the main pulmonary artery each showed a sudden increase in pressure. It is assumed that our patient also has bilateral constriction, since apparent constriction of both branches was

demonstrated on the angiocardiographic films, and there appears to be equal vascular markings in the two lung fields. The case described by Hodges, like three of the four published cases, and our own, all had pulmonary stenosis as an additional anomaly. This associated pathology may have importance in explaining the pathogenesis of the lesion, but at present the relationship is not clear. It is of interest that apparently all cases have had involvement of both branches of the pulmonary artery, although in the case of Shumacher and Lurie[2] and Sondergaard's[1] first case, the right pulmonary artery was not examined. Bailey[5] has described a narrowing of the main pulmonary artery which he labeled "coarctation" of the pulmonary artery. This appears to be a different entity from that described by Sondergaard and it is suggested the term be reversed for the latter condition, because of its possible common etiology with coarctation of the aorta. Further search for this condition will probably reveal additional cases and should help to clarify the pathogenesis of this and associated congenital lesions of the heart and great vessels.

SUMMARY

Sondergaard[1] has recently described three cases with bilateral constriction at the point of bifurcation of the main pulmonary artery. He has designated this condition as coarctation of the pulmonary artery. A similar case diagnosed by angiocardiographic and cardiac catheterization studies has been presented. This brings to six the number of cases that have been described. It is believed the suggested nomenclature should be adopted for describing this entity.

SUMMARIO IN INTERLINGUA

Recentemente Sondergaard describeva tres casos de constriction bilatere al puncto de bifurcation del major arteria pulmonar. Ille designava iste condition como coarctation del arteria pulmonar. Nos presenta un caso comparabile, diagnosticate per angiocardiographia e catheterisation cardiac. Isto augmenta le numero del casos describite a un total de sex. Nos opina que le termino proponite como description de iste entitate deberea esser adoptate.

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ARTERIOVENOUS FISTULA OF THE HEART

ROMAN KNOBLICH, M.D., AND ARNOLD J. RAWSON, M.D.

NORFOLK, VA.

ANOMALIES of the coronary arteries are rarities which can be divided into four groups: aneurysms, abnormal origin, absence or duplication, and arteriovenous fistulas. The arteriovenous fistula is the rarest of these, and although reported occasionally in animal hearts,[2,9] has previously been observed only three times in the human heart, proved by post-mortem examination. Halpert[5] described an arteriovenous communication between the right coronary artery and the coronary sinus with aneurysmal dilatation of the parts involved. This occurred in a 54-year-old man who died of cancer of the stomach and had no obvious disturbance of the heart during life, except for a systolic murmur at the apex. In Emminger's case,[3] an arteriovenous communication between the right coronary artery and the great cardiac vein was present in a 43-year-old woman who died in uremia and had no cardiac disturbance during life. Emminger quotes a similar case reported by Chiari. In two additional cases the diagnosis of arteriovenous fistula was established by surgical exploration. A 9-year-old boy, described by Paul[6] was operated upon to ascertain the origin of a continuous murmur, heard maximally over the lower right sternal border, and slight cardiac enlargement in the absence of electrocardiographic abnormalities. At operation an arteriovenous fistula connecting the right coronary artery and vein was discovered. No attempt at surgical correction was made and the patient was discharged in good health. Seven years later the patient was well and living a normally active life.[10] Paul appended a case of Gross' to his report, in which surgical exploration was performed on a 16-year-old boy because of suspected patent ductus arteriosus. A harsh continuous murmur associated with a thrill, maximal over the third and fourth intercostal spaces along the left sternal border was noted on physical examination. Exploratory operation revealed what was thought to be an arteriovenous fistula of the heart. The identity of the involved vessels was not ascertained, however. Eight years later the patient was well and living a normally active life.[4]

CASE REPORT

Mr. A. N., age 55, a businessman, was admitted in coma to Norfolk General Hospital following severe headaches of eight weeks' duration, more recently accompanied by vomiting. The patient was suffering from a known hypertensive cardiovascular disease with blood pressure as

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From the Department of Pathology, Norfolk General Hospital, Norfolk, Va.

high as 220/110 mm. Hg. On admission miosis of the pupils and flaccid paralysis of the upper extremities were noted. Blood was found in the spinal fluid and the diagnosis of ruptured intracranial aneurysm was made. He expired after being in coma for seven days.

Past history revealed that, at the age of 18, a heart murmur was noted, but he had never had rheumatic fever. He had been in good health up to ten years previously, when his blood pressure started to rise. X-ray examination at that time revealed cardiac hypertrophy. A peculiar harsh Grade 3 diastolic apical murmur of blowing character was noted on several occasions, and although never in failure, the patient had been digitalized in anticipation of the removal of a foreign body granuloma of the small bowel two years before the last admission. On April 25, 1952, three years prior to the last admission, an x-ray of the heart (Fig. 1) was described by Dr. K. K. Wallace as follows: Measurements: *M R* 4.1 cm., *M L* 12 cm., transverse aortic 4.8 cm., internal thoracic 30.4 cm. Diagnosis: Considerable myocardial enlargement with marked prominence of the left ventricular component. Subsequent x-rays revealed no significant change. An electrocardiogram on July 30, 1946, about nine years prior to the last admission, was reported as showing left axis deviation and minimal myocardial conduction change. Unfortunately these tracings were not available for study. Subsequent electrocardiograms six

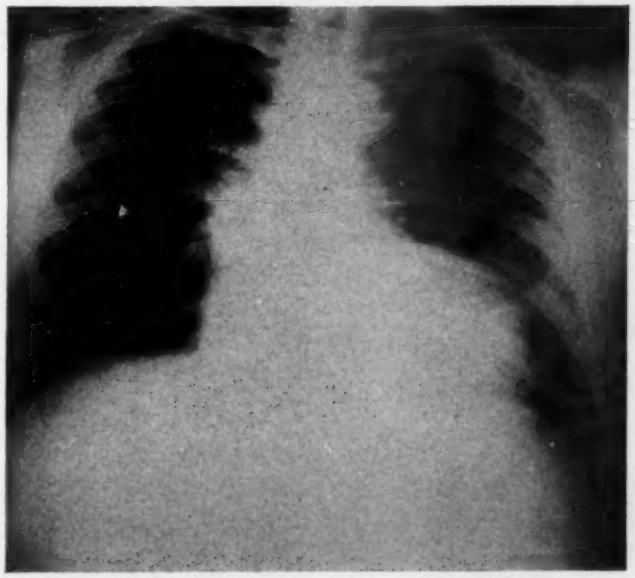

Fig. 1.—Distant heart plate, showing considerable enlargement of the heart with marked prominence of the left ventricular component.

years later on March 25, 1952, suggested myocardial damage and posterior infarction. Three years later on Sept. 17, 1955, the electrocardiographic recordings showed no significant change (Fig. 2). The interpretation by Dr. R. A. Morton follows:

> P: III, V_2 dicrotic; aV_R inverted; aV_L diphasic; V_4, V_5 notched; QRS: rSr′ in III and aV_F, small RV_4; Frequent unifocal ectopic beats; S-T: depressed and concave upward in I and aV_L; elevated and convex upward in II, III, aV_F, V_2, and V_4; depressed and convex upward in V_5; T: inverted in II, III, aV_F, and V_5; diphasic in V_4. Position: Horizontal, marked clockwise rotation. Impression: (1) Abnormal record; (2) Elevated S-T segments would indicate acute injury involving the posterior wall with anterior extension through the septum; (3) Frequent unifocal ectopic beats arising from septal region.

Subsequent electrocardiographic recordings revealed no significant changes.

Pathologic Studies.—

Autopsy diagnosis: (1) Congenital aneurysm of basilar artery with rupture and massive subarachnoid hemorrhage; (2) Necrosis of pons due to subarachnoid hemorrhage; (3) Hypertrophy of heart; (4) Nephrosclerosis, minimal; (5) Bronchopneumonia, minimal; and (6) Arteriovenous aneurysm of left coronary artery.

Description of Heart.—

The pericardium contains about 50 c.c. of straw-colored fluid. The heart weighs 600 grams. The great vessels have the usual origin. The ductus arteriosus and foramen ovale are closed. Both atria are normal. No lesions or abnormalities of the valves are noted. A large serpentine coronary artery is noted along the anterior longitudinal sulcus. The apex of the heart contains a bulging sacular structure. The left ventricle wall measures between 17 and 22 mm. in thick-

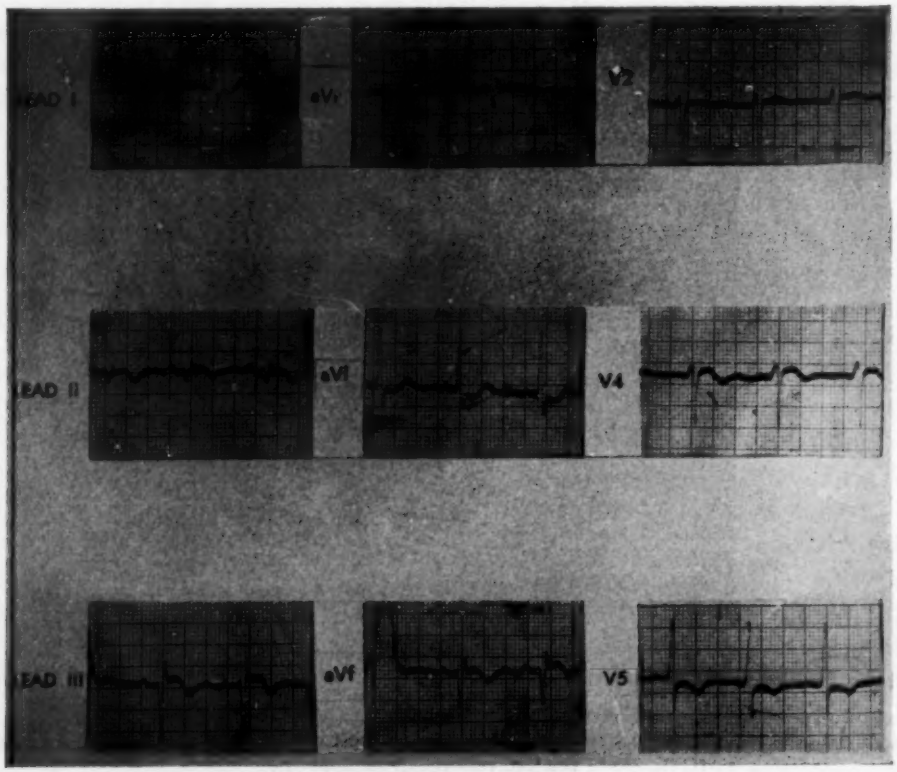

Fig. 2.—Electrocardiogram recorded Sept. 17, 1955; elevated S-T segments suggesting acute injury involving the posterior wall with anterior extension through the septum. Note frequent unifocal ectopic beats arising from septal region.

ness. The right ventricle measures 5 mm. in average thickness. The coronary arteries have the usual origin. The opening of the right measures 8 mm. in diameter, and the course is the usual one. The wall of the artery shows moderate involvement by arteriosclerotic plaques. The mouth of the left coronary artery measures 10 mm. in diameter. The vessel branches at the usual location into descending and circumflex branches. The circumflex branch is moderately dilated and takes the usual course. The descending branch after a tortuous course of about 5 cm. reaches its greatest diameter of 18 mm. (Fig. 3). The vessel is stiff with marked atheromatous changes and calcification. It runs across the enlarged apical portion of the heart, reaches the apex having a diameter of 10 mm. and continues its course along the posterior wall of the heart a short distance where it penetrates the heart wall and enters a sacular structure which is

entirely located within the apical portion of the septum. The sac measures 4.5 by 4.5 by 5 cm. and is lined by a thick, wrinkled, glistening grayish membrane (Fig. 4). The cavities of the right and left ventricle and the cavity of the sac are separated by 10 mm. of muscle. There is no connection between sac and ventricular cavities. Two centimeters above the entrance of the coronary artery into the sac, an opening 2 mm. in diameter is noted in a fold in the wall of the sac. A reddish friable thrombus 4 mm. in length is occluding the lumen. A channel 2 mm. in diameter lined by endothelium continues close to the wall of the sac into the heart muscle. After a downward course of 6 mm. the channel is no longer visible. No other gross lesion of the myocardium is found. Sections from the left descending artery prior to its joining the sac (*M*, *R*, *P* in Fig. 5) show an arterial wall with considerable arteriosclerotic involvement. Elastic fiber stains demon-

Fig. 3.—View of the anterior surface of the heart showing the tortuous, dilated descending branch of the left coronary artery. The diameter of the vessel averages between 15 and 18 mm. The vessel is stiff with marked atheromatous changes and calcification.

strate a prominent markedly scalloped internal elastic membrane. The tunica media is thick and well developed and demonstrates interlacing elastic fibers. Between the tunica media and the tunica adventitia is a well developed external elastic membrane. Sections from the sac (*N*) show a definitely venous character with thin fibromuscular wall and poorly developed scant elastic fibers. Sections from the small opening leading from the sac (*A*, *B*, *C*) by means of serial sections show a vein of gradually decreasing caliber which breaks up into dilated capillaries as the periphery of the myocardium is approached.

DISCUSSION

A reconstruction of the cardiac findings suggests that the course of blood flow was from the left descending coronary artery, through the sacular portion of the venous component, and out through the small venous branch in retrograde fashion. From the dilated capillary network into which the vein emptied, the blood apparently passed into normal venous channels. The dilated serpentine artery and the sacular vein are perhaps best explained on the basis of a markedly reduced capillary bed through which blood entering the terminal portion of the artery had to pass. A sharp angulation seems to account for the division of the vein into sacular and undilated components.

Fig. 4.—View of cross section through lower extremity of both ventricles. Within the septum is a sacular structure measuring 4.5 by 4.5 by 5 cm. Note the thick, wrinkled, glistening grayish membrane lining the sac. In the lower portion of the sac and to the right is a venous opening 2 mm. in diameter. Compare with diagram in Fig. 5.

The etiology of congenital arteriovenous anastomosis, in general, seems best explained on the basis of abnormal differentiation of the common embryonic anlage into artery and vein. It is believed[1] that arteries and veins differentiate from a common capillary plexus and that certain vessels which function as arteries at one stage of embryonic life may function as veins at another. At the beginning of the process of differentiation, multitudinous communications are present between arteries and veins, and the congenital type of abnormal communication between arteries and veins appears to be the result of persistence of the vessels of communication of the primary anlage, which fail to differentiate into the normal vascular tree, and form anastomotic channels either directly

or indirectly between otherwise normally developed arterial and venous trunks. As Reid[8] indicated, it is a marvel, not that congenital abnormal communications occur, but that they do not occur more often in view of the common bed of development of each side of the vascular tree, and the enormous constructive as well as destructive changes necessary before the final pattern is reached. With particular reference to the heart, Prinzmetal and associates[7] have demonstrated

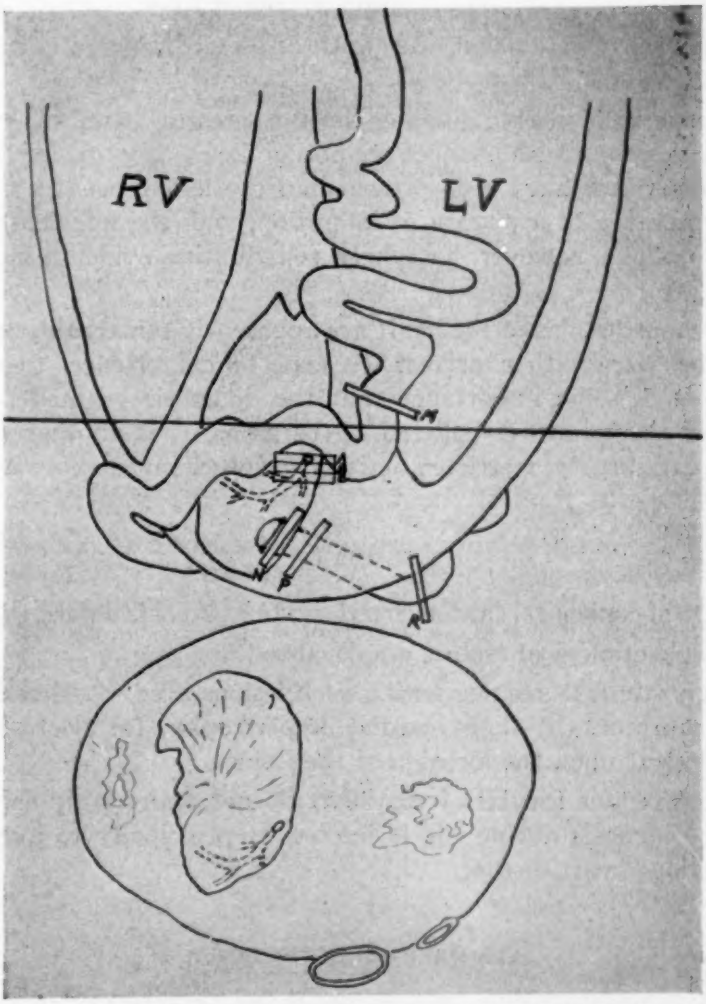

Fig. 5.—Diagram of the arteriovenous fistula. Microscopic sections from *M*, *R*, and *P*, show an arterial wall with considerable arteriosclerotic involvement. Sections from the sac at *N* show a definitely venous character with thin fibromuscular wall and poorly developed scant elastic fibers. Sections from the small opening leading from the sac (*A*, *B*, *C*) by means of serial sections show a vein of gradually decreasing caliber which breaks up into dilated capillaries.

the presence of normally existing anastomoses between both coronary arteries and the coronary venous system. This was demonstrated by the recovery of glass spheres 170 micra in diameter from the coronary sinus following injection into either coronary artery.

The harsh apical diastolic murmur, which in this case was first discovered at the age of 18, in the absence of rheumatic valvular disease seems to be one of

the diagnostic features. In the case reported by Paul[6] and that mentioned by Gross,[4] the principal physical sign was a continuous murmur with a prominent diastolic component of harsh character.

Considerable cardiac enlargement was present in our case and also in Halpert's case; slight enlargement was present in Paul's case. It is possible that the fistula may have resulted in significant myocardial strain over the course of time with consequent cardiac hypertrophy. In the present case, the presence of hypertensive cardiovascular disease must also be considered in evaluating the hypertrophy.

The electrocardiographic findings in the present case reflect the septal location of the lesion. Such changes are not, of course, specific for arteriovenous fistula, and would not have been present had the lesion been in a different location. The absence of a history of infarction, and the unchanging character of the pattern might, however, have been contributing evidence in favor of the diagnosis.

Arteriovenous fistulas of the heart are apparently remarkably well tolerated and do not interfere with a normal life expectancy. Hence, they require no therapy. It is of some importance that the diagnosis be made, however, in order to avoid the erroneous belief that the patient has another type of heart disease requiring surgery, restricted activity, or other interference with a normal life.

SUMMARY

1. A case of congenital cardiac arteriovenous fistula is described.
2. Possible etiological factors are discussed.
3. Diagnostic features suggesting such lesions are: (a) harsh continuous or diastolic murmur, (b) slight cardiac hypertrophy, (c) electrocardiographic findings dependent upon the location of the lesion.
4. Arteriovenous fistulas of the heart do not appreciably shorten the life span. Their diagnosis during life is important principally to avoid confusion with more serious heart disease.

SUMMARIO IN INTERLINGUA

1. Es describite un caso congenite de cardiac fistula arteriovenose.
2. Possibile factores etiologic es discutite.
3. Constatationes que suggere le presentia de tal lesiones es (a) continue o diastolic murmure rauc, (b) leve hypertrophia cardiac, (c) characteristicas electrocardiographic dependente del location del lesion involvite.
4. Fistulas arteriovenose del corde non resulta in notabile reduction del superviventia. Lor diagnose durante le vita del patiente es importante principalmente pro evitar lor misinterpretation como plus serie morbos cardiac.

Appreciation is expressed to Dr. M. R. Whitehill for permission to report this case.

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Announcement

A COURSE, "RECENT ADVANCES IN CARDIOVASCULAR DISEASES," is being held at The Mount Sinai Hospital, New York, Oct. 8 through 12, 1956, under the auspices of The American College of Physicians. The codirectors will be Arthur M. Master and Charles K. Friedberg. The fees for members of The American College of Physicians will be $30.00; for nonmembers, $60.00. Registration should be filed with the Executive Secretary, American College of Physicians, 4200 Pine St., Philadelphia 4, Pa.

Book Reviews

EXCITABILITY OF THE HEART. By Ch. McC. Brooks, B. F. Hoffman, E. E. Suckling, and Oscar Orias, New York, 1955, Grune & Stratton, Inc., 373 pages, 86 figures, and 13 tables.

In his foreword to the book, Carl J. Wiggers predicts that this monograph will be considered a classic by physiologists. As stated by the authors, "One of the major purposes of this monograph is to relate the modern theories concerning the origin of membrane potential and the processes of excitation and response to the study of the cardiac cell and the reactions of the heart." The book is, indeed, an up-to-date presentation of the fundamental processes of cardiac excitability during the cardiac cycle, their changes under the effect of intrinsic and extrinsic variables, and their relationship to mechanical events. Much of the experimental information has been obtained by the authors.

Although the book is essentially physiologic, it is invaluable for the clinician, particularly Chapters VI (The Production and Nature of Fibrillation), VII (Cardiac Reactions to Heat and Cold), VIII (The Effects of Heart Rate, Action of Autonomic Nerves and Chemical Mediators on Cardiac Excitability), IX (Fibrillatory and Antifibrillatory Agents), and X (The Effect of Inorganic Ions on Cardiac Excitability), pp. 131 to 303, which have rather immediate clinical aspects. The information in Chapters II to V is basic for electrocardiography (pp. 9 to 130). There is a summary at the end of each chapter which is very useful for quick orientation. The presentation of the difficult subject is very readable and fluid. Reading Dr. Wiggers' foreword, one expects much of the book, and this reviewer was not disappointed.

E. S.

DIAGNOSIS AND TREATMENT OF VASCULAR DISORDERS (ANGIOLOGY). Edited by Saul S. Samuels, Baltimore, 1956, Williams & Wilkins Company, 24 chapters, 621 pages, 366 figures, 27 tables.

The seventeen contributors to this book have been successful in dealing with the major peripheral vascular problems in a thorough and very practical manner. Emphasis upon the diagnosis and treatment of specific disorders has been achieved by means of careful discussions of anatomic, physiologic, and pharmacologic mechanisms.

Among the valuable features of the book are separate chapters devoted to methods of examination of the peripheral circulation, the techniques and applications of angiography, and the various methods and agents employed in anticcagulant therapy. Each of these chapters constitutes an excellent review and critique of the respective subject.

Much of the information contained in this volume may be obtained readily from other sources and many readers will be disappointed because of the omission of a number of the less common peripheral vascular disorders. Nevertheless the format, the numerous excellent illustrations, and the manner of presentation of the material should make this a popular and useful book.

J. W. E.